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MEETING  
OF THE  
SCIENTIFIC REVIEW PANEL ON TOXIC AIR CONTAMINANTS  
CALIFORNIA AIR RESOURCES BOARD

MILBERRY CONFERENCE CENTER  
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO  
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1 APPEARANCES

2 MEMBERS PRESENT:

3 Dr. John Froines, Chairman  
Dr. Roger Atkinson  
4 Dr. Paul D. Blanc  
Dr. Gary Friedman  
5 Dr. Anthony Fucaloro  
Dr. Stanton Glantz  
6 Dr. Hanspeter Witschi

7  
8 REPRESENTING THE CALIFORNIA AIR RESOURCES BOARD:

Mr. Jim Behrmann  
Mr. Bill Lockett  
9 Mr. Peter Mathews

10  
11 REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD  
ASSESSMENT:

12 Dr. Joseph Brown, Staff Toxicologist  
Dr. James Collins, Staff Toxicologist  
13 Dr. Melanie Marty, Senior Toxicologist  
Dr. Andy Salmon, Chief, Air Toxicology and Risk Assessment  
14

15 REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION:

16 Mr. Paul Gosselin, Acting Chief Deputy Director  
Dr. Robert Howd, Chief, Water Toxicology Unit  
17 Dr. Keith Pfeifer, Senior Toxicologist

18  
19 OTHERS:

Mr. Bruce Reeves, Attorney General's Office  
20  
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1 P R O C E E D I N G S

2 CHAIRMAN FROINES: So we shall officially call the  
3 meeting to order.

4 And the first item on the agenda is a discussion  
5 of substances to be included in the Air Toxic Hot Spots  
6 Program risk assessment.

7 So why don't we begin with Melanie Marty.

8 DR. COLLINS: Good morning, Dr. Froines. I'm  
9 James Collins, and I'm the chief -- I'm lead staff person on  
10 the chronic REL document here with Melanie Marty, chief of  
11 the Air Toxics Section, Epidemiology Section.

12 Today we're going to talk about three chemicals  
13 remaining from batch 2 A of the chronic RELs, and those  
14 three chemicals are chlorine dioxide, glutaraldehyde and  
15 1,3-butadiene.

16 In regard to chlorine dioxide, we used a French  
17 study. There were actually three separate studies on  
18 chlorine dioxide, and we came up with a value of .6  
19 micrograms per cubic meter.

20 During discussions, a member of the panel  
21 expressed concern that we had not used a human study  
22 published by Scandinavian workers in 1957.

23 And the reason we did not the use that study,  
24 because the authors themselves ascribed the adverse effects  
25 of chlorine dioxide to exposure excursions above the

1 reported mean level of .1 part per million. They did not  
2 specify how high the excursions were, but they were  
3 excursions.

4 So because of that, we decided it was safer to use  
5 the animal study at which several levels had been studied  
6 over a period of years.

7 If there are any -- and we added that statement  
8 from the workers into our summary of the adults, of the  
9 human studies.

10 If there are any questions about that.

11 DR. FUCALORO: I think it's fine.

12 I mean, just another small thing. Although right,  
13 the vapor pressure is 760 torr at the boiling point, it's  
14 superfluous. I mean I would just lose that.

15 DR. MARTY: So take out the "at."

16 DR. FUCALORO: No. I would just take it out  
17 completely, the vapor pressure, unless you do it at another  
18 temperature.

19 DR. MARTY: I see what you're saying. I'm sorry.  
20 Okay.

21 DR. FUCALORO: All that tells you is that vapor --  
22 the atmospheric pressure is 760.

23 DR. COLLINS: If there are any questions about --  
24 or any more comments about chlorine dioxide?

25 CHAIRMAN FROINES: I just have a quickie.

1           I assumed that the study that you quote, Ferris,  
2 1967, is a study at Harvard by Ben Ferris, and in which they  
3 looked at trace levels up to .25 parts per million, and I  
4 don't know what they then concluded with respect to average  
5 or the distribution of exposures, but you didn't use that  
6 study either. Can you just say a couple words about it?

7           DR. COLLINS: The problem with that study is they  
8 really looked at chlorine, more than chlorine dioxide. And  
9 some of the workers weren't even exposed at all to chlorine  
10 dioxide. So there was some exposure, but not enough that we  
11 thought you could make -- you could reasonably develop a REL  
12 from.

13           I have that study here with me.

14           CHAIRMAN FROINES: They're very solid  
15 investigators.

16           DR. COLLINS: I have that study. That's the  
17 problem. There was actually probably less exposure in that  
18 study than there was in the Gloemme and Lundgren study.

19           CHAIRMAN FROINES: Unless there are other  
20 questions, we should proceed.

21           DR. COLLINS: The next chemical is glutaraldehyde.  
22 In that study we used an NTP study. And the most sensitive  
23 sex and species was female mice. We developed a value of  
24 .08 micrograms per cubic meter using a LOAEL, UF approach.

25           And one of the panel members suggested or

1 requested us to evaluate data using the benchmark  
2 concentration approach.

3 We did use that approach, and we ended up with a  
4 revised value of .08 micrograms per cubic meter. So we  
5 ended up with the same number, but we ended up using an  
6 uncertainty factor of 30, rather than a hundred, and there  
7 is probably an improved estimate in using more of the data  
8 by using the benchmark concentration, so we ended up with  
9 the same result, but hopefully by a better method.

10 CHAIRMAN FROINES: Do you have any information --  
11 Mike Poor would be the person to ask, I guess, but has  
12 anybody looked at glutaraldehyde in the air?

13 DR. ATKINSON: Not that I know of. That's not an  
14 easy thing to see.

15 By the way, the vapor pressure that's given at 20  
16 degrees C looks awfully high to me, given that high volume  
17 point of 188. You might want to check that it's not 1.7.

18 DR. MARTY: Okay.

19 DR. ATKINSON: It could be 0.17

20 DR. MARTY: In regards to the air concentrations  
21 issue, we don't have concentrations available, but we do  
22 have from the air toxic hot spots California database on  
23 inventories the estimated emissions from stationary  
24 facilities is 29,600 pounds per year.

25 DR. ATKINSON: It's also formed in the atmosphere.

1 It's an atmospheric reaction product of cyclohexene.

2 DR. MARTY: That might actually be a larger  
3 contributor.

4 DR. ATKINSON: I don't know.

5 CHAIRMAN FROINES: This is one of the reasons that  
6 we want to have a session with Peter Venturini and other  
7 people to talk about priority setting, because this is a  
8 classic secondary pollutant in that sense of being formed in  
9 the atmosphere. And so at this level of .02 parts per  
10 billion, it's an interesting issue given that the squamous  
11 metaplasia, the respiratory epithelium -- what's the data on  
12 the carcinogenesis?

13 DR. COLLINS: I'm not aware that it's considered  
14 carcinogenic. I don't know whether I have that data with  
15 me. I could check it. I doubt that it's carcinogenic.  
16 It's certainly not something we have on our list as a  
17 carcinogen yet.

18 CHAIRMAN FROINES: I think the word "yet" may be  
19 the operative term. It's going to be fairly reactive. And  
20 the fact that you do see metaplasia suggests that you're a  
21 little bit on the way down the path of that.

22 This is -- these aldehydes are really important, I  
23 think, and it's something that hopefully we can take up as a  
24 class at some point, because I think they are so important.  
25 And we tend to focus on formaldehyde or acetaldehyde, and we



1 have a large range of other compounds, ranging from acrolein  
2 to glutaraldehyde and so on and so forth.

3 DR. COLLINS: The study, the summary I have here  
4 of NTP does not mention carcinogenesis, but they are  
5 concerned about the metaplasia and hyperplasia as possible,  
6 but it did not, from what I can tell, extend into  
7 carcinogenicity.

8 It's also true that the chemical was positive in  
9 several genotoxic tests including salmonella typhimurium.  
10 So that may also be a concern, cause for concern.

11 Is there any other question about glutaraldehyde?

12 Finally, I'd like to come to butadiene.

13 For the development of the chronic REL for  
14 butadiene, we also used a NTP study, and mouse was the  
15 species we used. We had an original value of 8 micrograms  
16 per cubic meter based on a LOAEL, UF approach with ovarian  
17 atrophy.

18 CHAIRMAN FROINES: What was the strain?

19 DR. COLLINS: I assume it's B6C3F1.

20 The original value was 8 micrograms per cubic  
21 meter. By using a benchmark concentration approach with the  
22 data, we ended up with a BMC 05 of 20 micrograms per cubic  
23 meter.

24 Based on Dr. Glantz's suggestion, we incorporated  
25 some information about arteriosclerosis in cockerels, due to

1 butadiene.

2           Today we want to address the panel's concerns  
3 about the kinetics of butadiene, especially how it might  
4 relate to an uncertainty factor.

5           So with the chairman's permission I'd like to  
6 yield ten minutes of my time to the honorable  
7 pharmacokineticist from OEHHA, Dr. Joseph Brown.

8           DR. MARTY: The issue that was raised was can we  
9 have a smaller uncertainty factor for interspecies  
10 extrapolation from the mouse to the human, because it's felt  
11 that the mouse probably makes more epoxide metabolite, which  
12 is the proximate toxicant to the ovary.

13           So we have actually an interspecies uncertainty  
14 factor of three, so we already lowered it from the guideline  
15 of ten, but we were asked by Dr. Witschi could we even lower  
16 it further, or do you even need one.

17           So we felt that we would like to stick to our  
18 interspecies uncertainty factor of three, and Dr. Brown is  
19 going to provide some description of the work he's done on  
20 looking at the kinetics of the epoxide formation.

21           DR. BROWN: Morning.

22           The main question here raised at the last meeting  
23 was why are we using the uncertainty -- interspecies  
24 uncertainty factor that we are, aren't mice a lot more  
25 sensitive than rats --

1           CHAIRMAN FROINES: Can you hear him in the back?

2           DR. BROWN: -- than rats or humans to the toxicity  
3 of butadiene.

4           This idea of this I think largely comes from the  
5 cancer bioassays that have been done. In the cancer  
6 bioassays mice have shown much higher tumor yields for a  
7 number of sites, particularly the lung and lymphoma in rats.  
8 In fact, the main study that's used has not even established  
9 an effect level for tumors, particularly lung tumor.

10          Rats showed tumors at different sites, testes,  
11 uterus, pancreas and mammary, so in some respects while it's  
12 clear that these tumors in the rats were observed in much  
13 higher concentrations, the fact that you're looking at  
14 different sites makes this comparison a little bit more  
15 complicated.

16          For example, in the mammary there is a fairly high  
17 background, but the incidence at the high dose is very high,  
18 and there's a very high multiplicity of tumors in the  
19 mammary gland of the rat.

20          So I think I've heard some people talk or in some  
21 papers that butadiene is almost noncarcinogenic in the rat.  
22 Well, it isn't.

23          There's also some data recently from a human  
24 occupational epidemiology study. The data are sort of weak,  
25 but they actually suggest a supralinear dose response.

1           The next slide shows --

2           CHAIRMAN FROINES:  When you say the data are weak,  
3   are you talking about that specific study, because I don't  
4   think it's fair to say that the epidemiology data on  
5   butadiene is weak.

6           Genevieve Matinowski and Carl Santos Brugoa in  
7   work, and others that have published over the years, was  
8   then -- much of the work was reanalyzed by Phil Cole, who  
9   duplicated the earlier work, and I think that there's  
10  greater, if you go through Bradford Hill's postulates,  
11  butadiene looks pretty reasonable carcinogen in human  
12  studies.

13          DR. BROWN:  Perhaps this is a toxicologist  
14  speaking about epidemiology data.

15          If you look at the -- this is from the Delzell  
16  report, not the publication, the actual report to EPA, they  
17  fit a number of dose response models to their data, and the  
18  authors concluded that this square root model, which gives  
19  sort of a supralinear response that has a higher slope at  
20  the lower cumulative butadiene exposure levels was the one  
21  that fit the data best.

22          Now, EPA in their 1998 draft report actually fit a  
23  linear model to those points.

24          So I guess I meant in the sense that the study,  
25  this study here, was done on males only in an occupational

1 setting and was weak from that point of view.

2 But as far as the epidemiology studies go, it's  
3 probably stronger than many other ones.

4 DR. MARTY: The relative risk would not be  
5 characterized as a weak effect.

6 CHAIRMAN FROINES: Yeah. I think that overall the  
7 epidemiology has grown considerably stronger over the last  
8 five years.

9 DR. BROWN: The next slide shows sort of a, I hope  
10 you can see this, this is sort of barred from -- if you turn  
11 it around the right way. You can see in the upper left-hand  
12 corner we have butadiene.

13 And just I wanted to point out here that a lot of  
14 metabolites have been detected in butadiene metabolism, but  
15 the ones that have been studied in most detail and are of  
16 most use and from the point of view of pharmacokinetic  
17 modeling, are the 1,2-epoxy-3-butene, what I call butadiene  
18 monoepoxide, that one in sort of the center of the screen  
19 there, with one epoxide group, and further on down the  
20 diepoxybutane, the DEB.

21 Also the glutathione conjugates have been studied  
22 in some detail, certainly in vitro preparations.

23 But there are a number of further downstream  
24 metabolites that have not been studied as well, and I'll  
25 talk about one of these later, later in the presentation.

1           But as you can see, there are three main types of  
2 metabolism, oxidation, conjugation, and hydrolysis, which  
3 lead to this plethora of metabolites.

4           The one in circles are the ones that are thought  
5 to be reactive in the point of view of possibly forming  
6 adducts with biological macromolecules.

7           Next slide, please.

8           Now, pharmacokinetic chamber studies and  
9 physiologically based pharmacokinetic modeling studies have  
10 shown that mice have much higher internal doses of butadiene  
11 monoxide, or BMO, for short, either as a peak mixed venous  
12 concentration, or as an area under the blood concentration  
13 times time curve, the AC, than is found in rats.

14           The difference is about 1.6 fold at butadiene  
15 exposure concentrations below 1000 parts per million, and  
16 two- to three-fold higher at higher concentrations, and  
17 there is evidence of glutathione depletion in the rats,  
18 which could lead to this explanation, partially explain this  
19 difference.

20           Medinsky in 1994 also did some modeling and  
21 metabolism, and they suggest a greater role for the lung  
22 metabolism at lower butadiene exposure concentrations.

23           In this case, the mouse BMO lung concentration was  
24 15-fold that of the rat after ten parts per million exposure  
25 to butadiene for six hours.

1           There's been a lot of elegant pharmacokinetic  
2 modeling done on butadiene over the years, but the bottom  
3 line here is there has really not led to an improved  
4 elucidation of the target tissue dosimetry, and more  
5 importantly the response, or the pharmacodynamic component  
6 here for the various endpoints in the rat, the lung, heart  
7 and malignant lymphoma.

8           Next slide, please.

9           A recent study, this time not with butadiene, the  
10 parent compound, but with the diepoxy metabolite, the DEB,  
11 showed upper respiratory cancer in rats, but not in mice,  
12 despite a twofold higher tissue dose to the mice. This is  
13 recently published by Henderson et al.

14           One conclusion here is that the butadiene  
15 pharmacokinetic models may not be sufficiently sophisticated  
16 and need to incorporate possibly more metabolites and  
17 certainly some sort of pharmacodynamic components, for  
18 example DNA repair.

19           The roles of other metabolites such as the  
20 diepoxybutene, diepoxybutane, the dihydroxybutene, the  
21 epoxybutanediol, and possibly even the conjugates of  
22 butadiene or even a minor metabolite such as crotonaldehyde  
23 or even the butene butenal, shown in the earlier slide, need  
24 to be defined, especially for other toxic endpoints.

25           Next slide, please.

1           This is a quote from the EPA's 1998 draft  
2 document, which is currently under revision. I looked on  
3 their Web site yesterday and I couldn't find any new  
4 information. I assume they are still revising this.

5           This refers to the carcinogenic endpoint that  
6 they're evaluating, and in the middle of that quote you can  
7 see that they say that any attempt to extrapolate the risk  
8 in rodents to humans, given the dramatic and unresolved  
9 interspecies differences between the mouse and the rat,  
10 would involve far greater uncertainties than basing the risk  
11 assessment on the occupational data of the Delzell et al  
12 study.

13           I'm not sure I would go that far, but this is  
14 their feeling, that they have actually in this draft  
15 assessment thrown out the animal data and basically based  
16 everything on this human study.

17           Next slide.

18           Okay. Basically the butadiene cancer dose  
19 response has been studied in more detail than any of the  
20 noncancer endpoints and to date we're not aware of any  
21 regulatory agency that's determined that humans are less or  
22 even equally sensitive than rodents for cancer or even other  
23 toxic endpoints.

24           Now, more pertinent to today's consideration, a  
25 variety of developmental and reproductive toxic effects, or



1 DART effects, have been seen in mice and rats exposed to  
2 butadiene by inhalation, testicular atrophy, ovarian atrophy  
3 and uterine atrophy.

4 In our current document or current draft document  
5 the chronic REL is based, as stated earlier, on a benchmark  
6 concentration at the five percent level of 1.4 parts per  
7 million for ovarian atrophy in mice.

8 We have calculated from this a human equivalent  
9 concentration of 0.25 parts per million, giving a CREL of  
10 the human equivalent concentration divided by these two  
11 uncertainty factors. The one that's in question, the  
12 threefold for interspecies and a tenfold for interindividual  
13 variation, giving eight parts per billion.

14 I want to point out here that the critical study  
15 is the same one used in the cancer data that had no NOEL  
16 determined at 6.25 parts per million. So we're actually  
17 extrapolating here to a value that's about five times lower  
18 for a NOEL based on benchmark dose methodology.

19 There are no human DART data on butadiene as far  
20 as I'm aware. So we're putting a lot of faith on this  
21 benchmark dose procedure.

22 Next slide.

23 Now, EPA in that same draft analysis that I  
24 mentioned earlier actually analyzed the same data set. They  
25 derived a human equivalent concentration of 0.38 parts per

1 million. As far as I can tell, the difference between the  
2 two values is that we corrected for the weekend off, the  
3 five over seven, and they didn't, I guess, and that's what  
4 looks like that's the difference between the two numbers.

5           Since the adverse effect has been linked largely  
6 to the amount of diepoxybutene metabolite in the target  
7 tissue, and this is in a separate study published by Doerr  
8 et al, where they exposed mice to DEB and also butadiene  
9 monoxide for 30 days, and since humans are expected to  
10 produce less DEB than mice overall, the agency concluded  
11 that they could use a smaller or less productive  
12 interspecies uncertainty factor of 1.5, allowing for some  
13 increased human sensitivity to DEB.

14           Doerr also found that BMO was ovotoxic to mice,  
15 but at higher concentrations, five- to tenfold higher doses.

16           So in this case there's sort of a disconnect here  
17 between, I guess, different people were doing the cancer  
18 assessment than the noncancer part, but the agency felt at  
19 least in the draft that they could live with a 1.5  
20 uncertainty factor.

21           Next slide, please.

22           Now, what about the DEB? Csanady et al in 1992  
23 found no BMO oxidation to DEB in human liver samples. These  
24 were surgical samples, 12 samples, or in five lung samples  
25 or in Sprague-Dawley rats. And they also found that the

1 mouse activity for the oxidation of BMO to DEB was  
2 relatively low, compared to the other metabolic steps that  
3 weren't analyzed.

4 More recently, Perez in 1997 found adducts of  
5 trihydroxybutyl valine, it's formed from the reaction of the  
6 epoxybutanediol with the internal valine of hemoglobin.  
7 This was found in in vitro preparations first and then in  
8 rats and also in humans exposed to butadiene by inhalation  
9 and also in the rats by intraperitoneal injection.

10 There also were a much lower level of monohydroxy  
11 adducts formed from butadiene -- excuse me, yes, from  
12 butadiene monoxide, but the major adduct formed was from the  
13 epoxybutanediol.

14 There's presently no adequate pharmacokinetic  
15 model to compare ovarian or uterine internal DEB or BMO  
16 dosimetry in mice versus humans, and there are no human data  
17 addressing this particular dosimetry issue.

18 I think the next slide shows -- this is a  
19 simplified metabolic scheme showing that you can get to the  
20 epoxybutanediol either through diepoxybutane or through the  
21 butenediol.

22 So just finding this adduct does not mean that it  
23 was formed from diepoxybutane, but at least there's sort of  
24 a 50/50 chance.

25 There's also some stereo isomerism in the products

1   formed, which can give you a hint about which side they  
2   might be coming from, but at least there's some indication  
3   that it's the DEB is formed in humans, or at least could be.

4               Next slide, please.

5               Now, we didn't have a lot of information on this,  
6   but despite this lack of pertinent information, we attempted  
7   to evaluate the ovotoxicity data of Doerr et al in mouse and  
8   human pharmacokinetic models. These are research models  
9   based on a number of published studies.

10              Although there are extensions of those studies  
11   that are published or validated in a proper sense, these are  
12   sort of research models to answer what-if questions.

13              There's a description, sort of a nonmathematical  
14   description, that I've attached to the handout.

15              What we did, we tried to simulate the ovotoxic  
16   intraperitoneal epoxide doses that were published from the  
17   Doerr study, and these doses were determined by Doerr were  
18   39.2 micromoles of butadiene monoxide per day, times 30  
19   days, and 3.9 micromoles of the DEB for 30 days.

20              And then what we did, we chose the metric of the  
21   area under the curve, the blood concentration, times time  
22   curved as the appropriate metric to use. So determined from  
23   the model now what metrics those doses would give, and we  
24   found that they would give metrics of 624 micromoles per  
25   liter times hours for BMO, and 36.9 micromoles per liter

1 times hours for DEB.

2 Then we asked, well, what sort of inhalation  
3 concentrations in these models would give those doses, and  
4 this is now in the mouse and human pharmacokinetic models.

5 And the results basically were for the mouse, 210  
6 parts per million times eight hours of exposure, would give  
7 a metric for butadiene monoxide equal to the 624 figure, and  
8 150 parts per million times eight hours will give a value in  
9 the human model for the DEB metric.

10 Now, I don't want to make too much out of these  
11 results. These are based on essentially taking the mouse  
12 kinetics and scaling them to humans.

13 And also it doesn't say anything about the  
14 response. We don't know anything about the response in  
15 humans.

16 But anyway you can see that the numbers are  
17 similar.

18 Next slide, please.

19 Essentially we view these various studies as  
20 indicating that there are still outstanding uncertainties in  
21 the interspecies dosimetry and response and that we think we  
22 ought to keep the threefold interspecies uncertainty factor  
23 for the ovarian atrophy.

24 My view is that you know this is already in our  
25 guidelines and we would need sort of very strong evidence to

1 the contrary for the toxic endpoint question to move away  
2 from that.

3 But I put these slides together to sort of frame a  
4 discussion so that the panel members would have a chance to  
5 check it out.

6 CHAIRMAN FROINES: Thank you.

7 Peter, I think you raised this issue originally,  
8 and so we should turn to you, in case you have further  
9 comments.

10 DR. WITSCHI: No, I don't have any further  
11 comments.

12 It's more on a real general basis, I think. You  
13 don't assume that people are more sensitive than the most  
14 sensitive animal species, but the data show this overall are  
15 really virtually nonexistent.

16 And so in the case of butadiene, I raised it  
17 because if people always do the default, even if you have  
18 data to the contrary, and then do all kind of things to  
19 still justify the default, to me that's not the very  
20 productive approach.

21 CHAIRMAN FROINES: I have a couple of comments.

22 Everything that Joe looked at, it's what I would  
23 call the front end of the process, and I think the part  
24 we're missing and we're going to need to think about it and  
25 talk about it in the future is how do we view this problem

1 when we consider GST polymorphism, because we know that  
2 humans have GST polymorphisms.

3 We know that -- I was at a meeting yesterday in  
4 which people were looking at the risk of lung cancer in  
5 males and females from an environmental tobacco smoke and  
6 the GST variation was really quite striking.

7 And so that when you have the so-called null  
8 allele of GST, the risk goes dramatically up with  
9 environmental tobacco smoke.

10 And so the heterogeneity of humans is really quite  
11 important to consider, and we tend to look at the issue from  
12 more classic toxicokinetic approaches rather than gene  
13 environment interaction.

14 And maybe some time in the future we can have a  
15 session and talk about how can we try and explore data  
16 that's in the literature that looks at the back end, at the  
17 lack of ability to conjugate these epoxides, so that they  
18 have a lot longer, a greater AUC and a longer residence  
19 time.

20 And that's why I would keep -- see, I would keep  
21 the risk factor of three, the uncertainty factor of three,  
22 precisely because I know that there are susceptible  
23 populations out there that do have GST markers that we  
24 aren't taking into consideration.

25 DR. BROWN: We did include in our modeling a

1 somewhat susceptible population. We used some data on obese  
2 young women, and we tried to model that, because we thought  
3 the higher body fat content would prolong this process of  
4 butadiene uptake and slow elimination, more chance for the  
5 area under the curve of the critical metabolites to be  
6 bigger, so we did include that in the analysis.

7 DR. MARTY: Joe, you guys didn't include the  
8 detoxification kinetics?

9 DR. BROWN: No.

10 DR. MARTY: And I think that's the point.

11 CHAIRMAN FROINES: And with work that we've done  
12 on looking at the interaction between MEK and hexane, we  
13 find that the interaction primarily occurs at the  
14 conjugation step, not at the bioactivation.

15 And so if one doesn't take into account the  
16 conjugation step, you actually miss the dominant competition  
17 between those two molecules, so it's -- let me just ask one  
18 more question and then I would go forward.

19 You said here in the document that the statewide  
20 mean outdoor monitored concentration of 1,3-butadiene was  
21 approximately .2 part per billion. And then you talk about  
22 the air toxic hot spots.

23 But I'd be curious to know what you know about hot  
24 spots or ambient levels in Southern California where the  
25 monitored concentrations are clearly not going to be as low



1 as .2 parts per billion, and so where does your eight part  
2 per billion, how does it relate to what we find in Los  
3 Angeles?

4 DR. MARTY: That's actually --

5 CHAIRMAN FROINES: Maybe Roger knows.

6 DR. ATKINSON: I don't know, but I would guess  
7 that it's less than eight, possibly more.

8 DR. MARTY: We can look that up and put that  
9 information in here.

10 CHAIRMAN FROINES: Does Lynn know?

11 FROM THE AUDIENCE: No.

12 CHAIRMAN FROINES: This is going to become one of  
13 these Froines litanies, right, that every time I see a  
14 document I'm going to ask what's in the air in LA.

15 So but it's obviously a relevant issue. It  
16 doesn't -- the statewide average concentration doesn't tell  
17 us what we need to know, I think.

18 DR. MARTY: The other issue is it's emitted from  
19 the tail pipe of vehicles and that's not included in the hot  
20 spots database, which is strictly stationary source.

21 CHAIRMAN FROINES: If you look at the Mates 2  
22 document, and look at the risk numbers at the LA airport  
23 from butadiene, they're quite high. So there's something  
24 about LAX that was -- caught AQMD's attention, so that there  
25 are obviously some hot spots that are not just vehicular

1 related.

2 So go ahead, Melanie.

3 DR. COLLINS: That completes our consideration of  
4 batch 2 A.

5 And I don't know whether the panel wants to -- has  
6 any other comments about the 20 chemicals in that batch.

7 DR. MARTY: We had some other small comments given  
8 to us that we haven't gone over, but we're making a few  
9 other small changes to the document total and then of course  
10 will go in as an addendum to part 3, our chronic reference  
11 exposure levels document.

12 CHAIRMAN FROINES: Okay.

13 DR. MARTY: So we need the panel's endorsement.

14 CHAIRMAN FROINES: We have endorsed the document,  
15 so unless -- we don't need to re-endorse these chemicals, do  
16 we?

17 DR. MARTY: This batch you haven't yet officially  
18 endorsed.

19 CHAIRMAN FROINES: No. I mean the ones that were  
20 dealt with today, I thought we'd already --

21 DR. COLLINS: It was continued for various  
22 reasons. It had been to be continued because of the  
23 organophosphate thing last time. You had to -- you didn't  
24 finalize it.

25 CHAIRMAN FROINES: So you need a vote from the

1 panel on the entire document and the issue we talked about  
2 with -- we're going to withdraw for this moment, methyl  
3 ethyl --

4 DR. MARTY: That's actually one that had already  
5 gone through the process, and we're going to talk about that  
6 in a second, but it's separate from this batch.

7 CHAIRMAN FROINES: Okay. So we need a motion to  
8 adopt these, the second batch of the chronic RELs.

9 DR. GLANTZ: So moved.

10 DR. WITSCHI: Second.

11 CHAIRMAN FROINES: Discussion?

12 All those in favor please say aye.

13 (Ayes.)

14 CHAIRMAN FROINES: Opposed.

15 (No response.)

16 CHAIRMAN FROINES: So the second batch is now  
17 approved by the Scientific Review Panel.

18 DR. COLLINS: Thank you.

19 CHAIRMAN FROINES: And thanks for the effort on  
20 this. I think that these were good questions that were  
21 raised.

22 And Peter particularly raised, I think, a very  
23 fundamental question that gets us out of the kind of  
24 lockstep approach to some of these things, and so that was a  
25 useful exercise. Don't you think?

1 DR. WITSCHI: Yes.

2 CHAIRMAN FROINES: Okay.

3 DR. MARTY: The next thing we wanted to talk about  
4 was we had a chronic exposure level developed for methyl  
5 ethyl ketone, which the panel had approved last February,  
6 and subsequent to the approval we received information from  
7 the Ketones Panel of the Chemical Manufacturers Association  
8 objecting to the use of the primary study that was the basis  
9 of the reference exposure level.

10 We met with the Ketones Panel in March, and we  
11 agreed to release the chronic REL for further comment.

12 The basis of that agreement was that the prior  
13 public draft was actually quite a bit different than the  
14 draft we ended up presenting to the panel, and which got  
15 approved, and so we felt that they were correct in being  
16 concerned that that draft had really not undergone public  
17 comment.

18 We then received comments from the Ketones Panel  
19 and from Dr. Graham Doyle from Vanderbilt, and we responded  
20 to those comments, and then presented the package to you  
21 several weeks ago, and are now bringing methyl ethyl ketone  
22 reference exposure level back to the panel.

23 So, Dr. Froines, I know you had some comment.

24 CHAIRMAN FROINES: Are you going to go further?

25 I had some agreements with the ketone folks.

1           I don't think that -- I don't think that one needs  
2   to -- historically, the toxicity of methyl butyl ketone and  
3   hexane have been characterized by their pathology, which  
4   Peter Spencer and Herbert Shamburg have called central  
5   peripheral distal axonopathy. And it's characterized by  
6   changes, particularly changes at the node of Ranvier and  
7   long nerves and degeneration distal to that.

8           And so that there was in the '70s and '80s, a  
9   whole series of compounds ranging from hexane to MBK to  
10   carbon disulfide to acrylamide and some organophosphates and  
11   others that fit into this pathologic pattern of central  
12   peripheral distal axonopathy.

13           And so that for a period of time, that type of  
14   neurotoxicity was considered relatively unique and people  
15   put a lot of time into studying the mechanisms of that  
16   particular neurotoxicity.

17           And Dr. Graham Doyle, Graham, was one of the  
18   leaders in that area of research.

19           And so there is some of the comments that were  
20   received, I fully concur with.

21           I think, however, that it's a mistake to in a  
22   sense say that neurotoxicity is limited to the kinds of  
23   changes that you see from hexane or MBK or some of these  
24   other compounds that have been so carefully studied.

25           So I think that one has to have a broader

1 definition of neurotoxicity than perhaps was used by the  
2 Ketone Panel.

3 So I would agree with OEHHA on that particular  
4 issue.

5 At the same time, I think the study that was used,  
6 the Mitran study, is extremely weak. It's weak  
7 statistically, it's weak in terms of the nerve conduction  
8 velocity measurements, and in general I think it's a study  
9 that as it sits out there by itself is very difficult to  
10 accept as a means to identify a REL for methyl ethyl  
11 ketone.

12 And so I personally feel that the current REL,  
13 based on the Mitran study, should be rethought, reconsidered  
14 by OEHHA, and then come back at a later time.

15 And I can go into more detail if you want, but I  
16 think that that's

17 DR. MARTY: We actually have an alternative REL  
18 based on animal studies. In fact, our original REL was  
19 based on animal studies.

20 So we can look at it now if you'd like, or bring  
21 it back to the panel at a later date.

22 It's based on Cavender study and Fischer rats and  
23 the critical effect is hepatotoxicity.

24 Andy, if you want to show the rest of it.

25 DR. GLANTZ: Wait, wait. Go back. Some of us

1 aren't good at speed reading.

2 DR. MARTY: There was not a NOAEL observed. The  
3 LOAEL was 1254 parts per million, six hours per day, five  
4 days per week for 90 days.

5 If you do a time-weighted extrapolation, that's  
6 equivalent to an average experimental exposure of 224 parts  
7 per million.

8 For a chemical with systemic effects, the human  
9 equivalent concentration is essentially the same.

10 DR. GLANTZ: What is RGDR, again?

11 DR. MARTY: Regional gas dose ratio.

12 DR. GLANTZ: What does that mean?

13 DR. MARTY: It's meant to account for differences  
14 in the rodent versus the human dosimetry in the lung.

15 DR. GLANTZ: That's once it gets there?

16 DR. MARTY: Yeah.

17 DR. GLANTZ: What's the number? Is it one? What  
18 you're saying here --

19 DR. MARTY: Because it's a systemic effect and not  
20 an impact on the lung or the respiratory tract.

21 DR. WITSCHI: What's the -- is the increased liver  
22 weight the only thing that was found?

23 DR. COLLINS: There were some other changes.  
24 There was increased liver weight in females at the three  
25 doses. There was an increased liver weight in males at the

1 highest dose. I think there was some increased brain weight  
2 in something. But it's not the only thing.

3 DR. WITSCHI: Was there any pathology?

4 DR. COLLINS: I'd have to check the thing. I have  
5 the paper.

6 DR. WITSCHI: That's been, on the other hand,  
7 that's been a very old bone of contention with increased  
8 liver weight as a toxic effect or an adaptive effect.

9 DR. COLLINS: I don't know. It's also dose  
10 related.

11 CHAIRMAN FROINES: Probably a reversible effect  
12 too.

13 DR. COLLINS: This is a 13-week study and they  
14 just did the animals then, so whether that was --

15 DR. MARTY: We applied a LOAEL uncertainty factor  
16 of three because it was considered a mild effect.

17 We have a subchronic uncertainty factor because it  
18 was only a 90-day study of three.

19 We have an interspecies uncertainty factor of  
20 three and an intraspecies uncertainty factor of ten with a  
21 total cumulative uncertainty factor of 300. This gives you  
22 a chronic inhalation REL of 2000 micrograms per cubic meter  
23 or .7 PPM.

24 DR. GLANTZ: How does that compare with the one  
25 you had before?



1 CHAIRMAN FROINES: 200 versus 700.

2 DR. GLANTZ: Pardon me?

3 CHAIRMAN FROINES: 200 versus 700.

4 DR. MARTY: Right. 200 parts per billion versus  
5 700 parts per billion.

6 The study basically states that they didn't  
7 attribute any histopathology of the liver to MEK, but that  
8 the pathology was normal age-related pathology for Fischer  
9 rats.

10 So it is just increased liver weight.

11 I think if we had seen pathology, we would not  
12 have considered it a mild effect.

13 CHAIRMAN FROINES: I would suggest that we go back  
14 to the drawing board on this one.

15 DR. MARTY: That's fine.

16 CHAIRMAN FROINES: And consider it further,  
17 because I don't think anybody is going to be very happy with  
18 the pathology that you just described.

19 DR. MARTY: Okay. Why don't we roll it into our  
20 next batch.

21 CHAIRMAN FROINES: Peter, do you agree with that?

22 DR. WITSCHI: Yeah.

23 DR. MARTY: Why don't we roll MEK back into our  
24 next batch and we'll officially withdraw the existing REL.

25 Actually OEHHA never adopted that REL because of

1 the concerns brought up by the Ketones Panel.

2 CHAIRMAN FROINES: This isn't a criticism, it's  
3 really an honest question. There must be a lot of studies  
4 on neurobehavioral effects of MEK over the years, I would  
5 assume. And I gather that you haven't found much. I just  
6 would assume that people who look at neurobehavioral effects  
7 of solvents would have looked at MEK, because, you know, the  
8 one thing that's true about it is that it's very widely used  
9 in industry, so that there is a lot of exposure to MEK.  
10 It's just not a very toxic compound. It has air pollution  
11 implications that are different than its own inherent  
12 toxicity.

13 DR. SALMON: I think one of the problems is that  
14 because it is known to be a relatively nontoxic chemical,  
15 people have not paid a great deal of attention to it. It's  
16 certainly one problem.

17 Certainly there are neurobehavioral or  
18 neurosensory effects reported after a fashion in the Mitran  
19 study, for instance, which was probably a better endpoint to  
20 look at, other than nerve conduction results from some  
21 standpoints.

22 But nonetheless I think we have to look very hard  
23 to find a good basis for a REL for this compound because the  
24 data on it isn't as good as you would hope.

25 DR. MARTY: Most of the studies that were done

1 looked at potentiation of the neurotoxicity of other  
2 chemicals.

3 CHAIRMAN FROINES: Well, I think it's also good if  
4 we can get Stan to look at the Mitran study, because I think  
5 the statistics are almost nonexistent, and so it's very hard  
6 to trust the comparisons that they report.

7 DR. MARTY: Right. They did statistics only on  
8 the nerve conduction velocity data, but not on their other  
9 data.

10 We did some statistics on their other data and  
11 found significant impacts, but again it's -- those are  
12 difficult to interpret that data, symptomatic type thing.

13 CHAIRMAN FROINES: I think in terms of the --  
14 accepting a document that's in the peer reviewed literature,  
15 I think the panel would prefer to have documents in which  
16 the authors had done some statistics that was then peer  
17 reviewed.

18 It's great that you folks come in and do your own  
19 statistics, but it seems that the research papers should  
20 have had that within it to be considered. In fact --

21 DR. MARTY: I agree.

22 CHAIRMAN FROINES: -- one can honestly ask the  
23 question how did it ever get through a peer review process,  
24 given the quality of this paper.

25 It's Environmental Research, so it's a reasonable

1 journal.

2 DR. COLLINS: One of the reasons was it appeared  
3 in a symposium several years ago, and I think the journal  
4 relied on the people in the symposium to send them something  
5 credible.

6 CHAIRMAN FROINES: Oh, so it may end up being not  
7 really peer reviewed.

8 Because I would urge, since some of the panel  
9 members probably haven't looked at the paper very carefully,  
10 I'd urge you to look at it and make sure that you agree with  
11 what I'm saying.

12 But, to your credit, you didn't claim it to be the  
13 end-all be-all when you wrote your response to the ketone  
14 committee.

15 So let's go back and see what we can come up with.

16 And I think Andy is right, the problem is that  
17 this is nontoxic and nobody -- but you would have assumed  
18 that the Swedes would have at some point or the Finns would  
19 have looked into it. They've looked at all these solvents.

20 Okay.

21 DR. MARTY: Okay. I think that concludes our REL  
22 agenda item.

23 DR. COLLINS: Thank you.

24 CHAIRMAN FROINES: We're altering the agenda.

25 We have a problem that Paul Blanc can't be here

1     until about noon, and so what we're going to do is -- and  
2     the closed session we consider to be a very important  
3     meeting for the panel, since there are two suits pending and  
4     a third administrative procedure, so we want to take that up  
5     as soon as we can.

6             But we wanted Paul to be here for that, since it  
7     does concern him.

8             So we hate to have a legal discussion about a suit  
9     or two suits without one of the key players able to hear and  
10    participate in the discussion.

11            But so at this point I'd like to move on to the  
12    overview of Senate Bill 25, which I think is more  
13    informative for information purposes than having any major  
14    decisions on the part of the panel.

15            Has everybody on the panel been sent this summary  
16    document, Peter?

17            DR. GLANTZ:   Which summary document?

18            CHAIRMAN FROINES:   This SB 25.

19            DR. GLANTZ:   No.

20            CHAIRMAN FROINES:   It wasn't?   That's an  
21    oversight.   I'm sorry.   Hopefully we'll cover it and then we  
22    can get you the document.

23            DR. MARTY:   Okay.   This is Melanie Marty from  
24    Office of Environmental Health Hazard Assessment.

25            I'm just going to give a fairly brief overview of

1 Senate Bill 25, which was written by Martha Escutia last  
2 year in the past. It's called the Children's Environmental  
3 Health Protection Act.

4 And I'm going to go through -- the first slide  
5 will be just a very brief overview just to give you an idea  
6 of the breadth of the act, and then mostly talking about the  
7 role of the OEHHA and the panel for the remainder of the  
8 slides.

9 The requirements of the act include -- the basis  
10 of the act is to get people to look specifically at infants  
11 and children when setting ambient air quality standards for  
12 the criteria air pollutants when evaluating health effects  
13 of the toxic air contaminants, but it also includes trying  
14 to look at our air monitoring network that the Air Resources  
15 Board already has set up and evaluating whether that's  
16 adequate to really measure exposure of children, and it  
17 requires monitoring at specific areas where there are  
18 children.

19 There's also provisions in there for the South  
20 Coast Air Quality Management District to notify day care  
21 centers when standards are exceeded.

22 And it also created a children's environmental  
23 health center that is in Cal EPA.

24 I did mention already that we are reviewing all  
25 existing health-based ambient air quality standards to

1 determine whether they adequately protect the health of the  
2 public, including infants and children. There isn't any SRP  
3 involvement, but I did want you to know that was going on.  
4 It's a big deal.

5 We actually already have gone through a  
6 prioritization process to prioritize for re-review that  
7 underwent public comment and peer review by the Air Quality  
8 Advisory Committee, and tomorrow will be an item at the Air  
9 Resources Board just to adopt the order in which the  
10 chemicals will be reevaluated.

11 So that's all I'm going to say about the criteria  
12 pollutants.

13 The statute requires OEHHHA to list up to five  
14 toxic air contaminants that may cause infants and children  
15 to be especially susceptible to illness and we have to  
16 create this list by July 1st, 2001, and the SRP is  
17 responsible for reviewing the report containing the  
18 justification for the chemicals on the list.

19 DR. GLANTZ: When you say up to five toxic air  
20 contaminants, does that mean of the ones that are already  
21 identified?

22 DR. MARTY: Yes.

23 CHAIRMAN FROINES: Can I ask a question about  
24 that?

25 DR. MARTY: Sure.

1           CHAIRMAN FROINES:  When you're making up -- when  
2   you're making this determination that children are  
3   especially susceptible to illness, at some point are you  
4   going to describe for us what the criteria for that  
5   determination is going to be?

6           DR. MARTY:  Yes.  It will be in the report that  
7   you folks review.

8           CHAIRMAN FROINES:  So that the actual methodologic  
9   approach will be reviewed by the panel as well?

10          DR. MARTY:  Yes.

11          CHAIRMAN FROINES:  Gary.

12          DR. FRIEDMAN:  One thing I'm not clear about is  
13   whether the illness must occur during infancy and childhood  
14   or whether if the person when they're exposed at a very  
15   young age is especially susceptible to getting something 30  
16   years later, is that also --

17          DR. MARTY:  That's included, yes.

18          DR. FRIEDMAN:  Are both of those?

19          DR. MARTY:  Both those concepts are included in  
20   the way we're looking at it.

21          DR. FRIEDMAN:  Okay.

22          CHAIRMAN FROINES:  My question is actually  
23   different than that.

24                 My question is when you look at that, are you  
25   going to consider different routes of exposure as well as



1 the toxicologic side of it?

2 DR. MARTY: Yes. Actually the next slide might  
3 clarify some of that.

4 It actually states in the statute that when we're  
5 evaluating chemicals we have to look at exposure patterns  
6 that might result in disproportionate exposure of infants  
7 and children. For example, kids have much -- toddlers have  
8 must greater mouthing behavior than an adult, so oral  
9 exposures can be much greater in a child than in an adult.

10 Likewise for chemicals that are heavier than air,  
11 the exposures closer to the ground, the concentrations  
12 closer to the ground are heavier, and you can get very large  
13 differences in the inhalation exposure to an adult versus  
14 the inhalation exposure to a toddler standing in the same  
15 room.

16 So those kinds of things need to be accounted for.

17 The statute requires us to account for special  
18 susceptibility of infants and children, and this gets at the  
19 idea of windows of susceptibility during development of  
20 organs.

21 And effects of exposure to pollutants with common  
22 mechanisms of action, we do do that right now with our  
23 hazard index approach, so we'll be looking at the hazard  
24 index approach again.

25 And finally the statute requires us to not -- they

1 didn't want us to look at criteria air pollutant in a  
2 vacuum, and toxic air contaminants in a second vacuum, so is  
3 there interactions between the two.

4 DR. FRIEDMAN: What's the difference between the  
5 two?

6 DR. MARTY: The criteria pollutant are those  
7 chemicals which have actual levels which are standards not  
8 to be exceeded, and they are generally the major components  
9 of what we think of as smog. So particulate matter, carbon  
10 monoxide, ozone, nitrogen oxide, sulfur oxides.

11 And then I think there's a couple more. Hydrogen  
12 sulfide is one.

13 We actually have a criteria for lead, but lead is  
14 also dealt with in the toxic air contaminant program, and we  
15 intend to deal with it in the toxic air contaminant program  
16 for this process, rather than reevaluating a lead ambient  
17 air quality standard.

18 It was a little more important when there was lead  
19 in gasoline. It's more of a hot spot issue now rather than  
20 a general ambient issue.

21 The ramifications of developing this, creating  
22 this list, is that within two years of the creation of the  
23 list, the Air Board has to reevaluate their airborne toxic  
24 control measures for any of the chemicals that make the  
25 list.

1           So in other words, by July 1st, 2003, if a  
2 chemical makes the list which does not have an airborne  
3 toxic air control measure, or an ATCM, then the Air Board  
4 must develop one within three years of the listing of that  
5 chemical.

6           CHAIRMAN FROINES: Would that mean that the Air  
7 Board would actually reconsider controls on point sources as  
8 well as ambient?

9           DR. MARTY: Yes.

10          CHAIRMAN FROINES: For lead, say?

11          DR. MARTY: Yes.

12          DR. FRIEDMAN: Was the reason to limit this to  
13 five so as not to overburden you, or what?

14          DR. MARTY: Exactly.

15          DR. FRIEDMAN: Maybe you can go through and  
16 find -- if you found like six really important ones you just  
17 don't -- you can't do the sixth?

18          DR. MARTY: Well, we can, because we're allowed to  
19 update the list.

20          But the initial statute required up to five, and I  
21 think ARB would really appreciate it that it be no more than  
22 five the first time around, because of this measure that  
23 they have to deal with looking at the airborne toxic control  
24 measures.

25          Okay. Jim.

1           The progress to date, we started out with all of  
2   the TACs that are already identified, and we went through a  
3   prioritization process based on amount of emissions, the  
4   toxicological data availability and the toxic endpoints. In  
5   other words, for the toxic endpoints if it was something  
6   like an eye irritant, we would be less concerned than if it  
7   was a neurotoxicant, because children are likely to be more  
8   sensitive to most neurotoxicants than adults, so we  
9   considered that.

10           We ended up skinnying down the list to 33, so we  
11   made a cut at 33 TACs, which we selected for focused  
12   literature reviews of the toxicology and epidemiology  
13   literature to see if there are any indication whether  
14   infants and children might be more susceptible to that  
15   compound than adults.

16           DR. GLANTZ: Do you have the list of the 33?

17           DR. MARTY: We do, but it hasn't been released.

18           The literature reviews are currently being  
19   conducted. Some of them are in house, but most of them are  
20   by contract by UC, various UC people.

21           CHAIRMAN FROINES: So that Kent Pinkerton at Davis  
22   is doing a lot of work on animal models that look at  
23   developmental changes associated with particulate matter  
24   exposure, so PM could be one of the --

25           DR. MARTY: PM actually we're dealing with a

1 criteria air pollutant, so we did have Kent involved in that  
2 part of the process.

3 The next steps are to collect literature reviews  
4 of all 33 chemicals and study those reviews, and then  
5 further winnow down the list and select ten, based on the  
6 likelihood of having potentially differential impacts on  
7 children relative to adults.

8 Then we will prepare the report providing the  
9 criterion and the justification for the listing choices and  
10 release that for public comment.

11 OEHHA then will respond to public comment and  
12 bring the report and the comments and the responses to the  
13 panel.

14 And SRP will review this report, provide comments  
15 to us, and input to the selection of the first five TACs.

16 Then we will revise our report based on the panel  
17 comments and submit it to the Air Resources Board. This has  
18 to be done by July 1st.

19 CHAIRMAN FROINES: We'll get ten?

20 DR. MARTY: You'll get ten. You'll get ten.

21 Actually it may be a little more than ten, so  
22 there's some wiggle room in there, depending on what we see  
23 in the reports that we get back, which is -- we've gotten  
24 three back. We're getting 30 more this month.

25 So what the panel will see from OEHHA, I broke it

1 down between 2001 and 2004, and then 2004 and beyond.

2 Initially the report describing the criteria for  
3 identifying which chemicals may differentially impact  
4 children, you will see that hopefully by March, the  
5 beginning of March. This will include the list of the ten  
6 candidates or maybe a little more, and also our responses to  
7 public comment.

8 As part of this process we are actually being  
9 required to go back and look at the health evaluations we've  
10 done for the toxic air contaminants and decide whether they  
11 adequately protect children.

12 DR. GLANTZ: What is the CPF?

13 DR. MARTY: Just a second. I'll get there.

14 DR. GLANTZ: I'm sorry.

15 DR. MARTY: So as part of that process we are  
16 evaluating our existing methodologies that we use to develop  
17 cancer potency factors, CPF, or unit risk factors, and  
18 reference exposure levels for adequacy in protecting  
19 children.

20 We have to do this before July 1st, 2004.

21 The panel is going to review any proposed  
22 revisions to our health risk assessment methodology that we  
23 think we need to make in order to adequately protect infants  
24 and children.

25 And so that will be happening more like 2002

1 through 2003.

2 Then beginning July 1st, 2004, OEHHA needs to  
3 annually evaluate at least 15 TACs and provide threshold  
4 exposure levels. That's the legal term. We just call those  
5 reference exposure levels.

6 And non-threshold health values as for the  
7 carcinogens, e.g., the cancer potency factors, if that's  
8 appropriate, for each of the 15 toxics.

9 And then the panel has to review our evaluations  
10 of the health effects of those toxics.

11 CHAIRMAN FROINES: Is there a time table? Is that  
12 15 per year?

13 DR. MARTY: Per year. It's 15 per year.

14 CHAIRMAN FROINES: 15 per year?

15 DR. MARTY: He's laughing now.

16 CHAIRMAN FROINES: We want a raise.

17 DR. MARTY: The activities are scheduled to  
18 continue until all the TACs have been evaluated.

19 And also I wanted to add that OEHHA shall update  
20 the list by July 1st, 2005, so they have a provision in  
21 there to update the list. They've given us a few years to  
22 work out methodologies and the list update follows the  
23 review of the health evaluations by the panel.

24 This is just a time line. I can provide copies of  
25 the time line to the panel. Actually we should have

1 attached them to the handouts.

2 Just gives you an idea for this first set of five,  
3 what we're doing and where we are. We started out with all  
4 of the TACs and then I mentioned we eliminated certain ones  
5 based on really lack of data on toxicity or exposure, got  
6 down to 90. Skinnied that down to 33. The literature  
7 reviews are ongoing.

8 We are developing the document as I speak.

9 And we will be preparing then a summary of at  
10 least ten, possibly up to 20, chemicals for public input and  
11 then review by the panel to decide which five chemicals  
12 should make the first cut.

13 So it's a lot of work in the next six months,  
14 basically.

15 DR. WITSCHI: Have you already developed some  
16 criteria how you're going to identify those five? I mean,  
17 is it going, for example is it is going to be very toxic to  
18 just a few, or something that's not really that toxic but  
19 might effect many? All those kinds of things.

20 DR. MARTY: All of that comes into play. If it's  
21 very toxic, but there are hardly any emissions, then it  
22 would rank lower than something that is fairly toxic with  
23 lots of emissions and exposure.

24 And we actually did that first when we did that  
25 first cut of the TACs. We based it on emissions, times



1 toxicity. So we used the same method that ARB uses to  
2 prioritize their candidates for TAC.

3 DR. WITSCHI: Yes. What is the first thing we are  
4 going to see, because I would like to see all 90 to begin  
5 with and then the 33 and then your five.

6 I'm not saying I would like to do the work in  
7 ranking them, but I would like to see everything that you  
8 have considered, simply because once in a while one of us  
9 might have additional opinion on where something belongs.

10 DR. MARTY: We're going to describe everything  
11 we've done in the report that you get.

12 So if you disagree with our -- and the reason  
13 we're providing not just five for you to look at, but ten to  
14 20 is because we know that there's going to be people who  
15 think one of these is more important than another, and we  
16 need to hear that.

17 But we probably will actually end up if we gave  
18 the panel the same chemicals and told them to do the same  
19 thing, we'd probably end up with about the same top 20 or 30  
20 anyhow. That's my guess.

21 DR. WITSCHI: Have you looked at this report that  
22 was issued, it was about five or -- five or eight years ago.  
23 I think it was called comparative risk or relative risk,  
24 where it was a huge committee which tried to rank all the  
25 agents which are around us, and I was on that one. I was

1 actually on two of them.

2 DR. MARTY: The comparative risk report?

3 DR. WITSCHI: Yes.

4 DR. MARTY: The comparative risk?

5 DR. WITSCHI: Yes.

6 DR. MARTY: Yes. We have that.

7 DR. WITSCHI: That should give you some idea of  
8 what you might get into.

9 DR. MARTY: We have that.

10 There are also actually a number of publications  
11 that have come out looking at children as susceptible  
12 subpopulations, and the reasons why that might be. So we're  
13 looking at all that information also.

14 DR. WITSCHI: I wasn't referring to the relative  
15 risk report with regard to children. I was referring to it,  
16 how incredibly complex and difficult and next to impossible  
17 it is to rank any of those things.

18 DR. MARTY: Yes. Yes. That report had nothing to  
19 do with kids actually. It was just is this thing more risky  
20 than that thing.

21 DR. WITSCHI: The other one is this was about ten  
22 years ago, the US EPA came up with unfinished business, and  
23 the Health Effects Panel, of which I was a member, couldn't  
24 come up with any intelligent ranking.

25 And the most interesting thing which came out of

1 the unfinished business report is that the people really had  
2 something to say what was bad and what was not so bad, were  
3 people who dealt with the environment, but not with the  
4 health effects.

5 The health effects were stymied because we  
6 couldn't say what's more important, ozone or maybe lead or a  
7 cancer agent where we know there's only very little around,  
8 as opposed to an air pollutant which might not cause that  
9 much, but there's a lot around.

10 DR. MARTY: We're obviously not in as envious a  
11 position as people who work on criteria air pollutants,  
12 because they have lots of epi data and they have lots of  
13 data on kids, but there are certain compounds where there  
14 have been a lot of data. Lead is one of them. And in fact  
15 the basis of our TAC document, as you'll recall, impacts on  
16 children.

17 So the first five are likely to be chemicals where  
18 there is a reasonable amount of actual hard data that  
19 indicate kids are differentially impacted relative to  
20 adults.

21 DR. WITSCHI: You said for children. I think if I  
22 get that one, you said the concentrations are lower where  
23 they breathe? The breathing zone of toddlers.

24 DR. MARTY: If a chemical is heavier than air, it  
25 tends to be more concentrated in if you're in a room, the

1 lower down you are --

2 DR. FUCALORO: Like a solid.

3 DR. WITSCHI: I know that.

4 Is it really established that there's a breathing  
5 zone for toddlers which is --

6 DR. ATKINSON: I wouldn't have thought you would  
7 find that unless it's in an enclosed area with almost no air  
8 movement.

9 DR. MARTY: Yes. It's generally been found in a  
10 closed area.

11 For example, there's a somewhat famous report of a  
12 house being painted with latex paint that had mercury as a  
13 fungicide and a three-year-old in the house came up with  
14 signs of mercury toxicity, where the adults and an older  
15 sibling were unaffected.

16 DR. WITSCHI: There's actually one spectacular  
17 incident about this thing being heavier than air, and this  
18 was about when 15, 20 years ago, this lake in Africa, which  
19 blew up, and the carbon dioxide spilled over and about 1500  
20 people died.

21 DR. FRIEDMAN: I'm just curious, when you get a  
22 new major responsibility like this from the Legislature, do  
23 they also give you added resources to carry it out or will  
24 this cut into your other work and we can expect slower  
25 production of other reports that you had planned in the

1 past?

2 DR. MARTY: Well, when we get another  
3 responsibility from the Legislature, we are given the  
4 opportunity to what they'd call a bill analysis, and part of  
5 the bill analysis is an estimation on our part of how much  
6 we think it's going to cost to do that.

7 And then we have to go through the channels to get  
8 the money approved. Very rarely do they actually put the  
9 appropriations in the bill anymore, because it won't pass if  
10 they do that.

11 So you go through another set of processes to get  
12 the money from the Department of Finance.

13 But I can tell you that we got I think less than  
14 half what we asked for.

15 So it does impact on other things that we're  
16 doing.

17 At the same time this is an amendment to the  
18 statute that set up the toxic air contaminant process to  
19 begin with. So it just adds it to the TAC process, but  
20 we're already looking at that stuff anyway. We're just  
21 going to be doing more efforts to focus on children, both  
22 from the exposure standpoint.

23 And we did do some of that in our exposure  
24 document for the hot spots, where we had for chronic  
25 exposure we had separated out children from adults and when

1 we developed our distributions and our point estimates.

2 So we have done a little bit of that already.

3 DR. FRIEDMAN: This panel I know is always putting  
4 pressure on the agencies to produce reports in a timely  
5 fashion. As a result of this new assignment, should we  
6 expect that other reports will be coming more slowly or that  
7 they should be coming at the same rate of speed?

8 DR. MARTY: I think they will be coming a little  
9 more slowly.

10 So, for example, if we're asked to do a toxic air  
11 contaminant report on a new unidentified TAC, it's going to  
12 be difficult to fold that into this process, time wise.

13 CHAIRMAN FROINES: Well, it's following up on what  
14 Gary is saying, having been here since the beginning of this  
15 process, in the beginning, you know, we took benzene and we  
16 did benzene, and that was a major effort.

17 And then we did ethylene dibromide and that was an  
18 effort.

19 But since that time, since we've been doing  
20 chemical by chemical, we've added pesticides that we now are  
21 putting enormous effort in. We've developed a certain  
22 number of workshops that we hadn't done before. We had your  
23 acute and chronic RELs. We have added the methodology for  
24 risk assessment. And now we're adding SB 25.

25 So that one of the problems is that we've added an

1 enormous number of responsibilities to this panel, and there  
2 is a question about how do we function as an advisory panel  
3 within that particular context, because clearly one of the  
4 good things is people respect this panel, so they give us  
5 work to do. But as long as they keep respecting us and keep  
6 giving us work, we're still the same group of nine people  
7 who meet on average once every couple of months.

8           So we don't get the same actual improvement in  
9 resources that you all do.

10           So it's -- I'm a little concerned about, which I  
11 think is your implication too, of that we become, you know,  
12 what's that tunnel in going into Walnut Creek, we become  
13 the --

14           DR. MARTY: Caldecott.

15           CHAIRMAN FROINES: -- the Caldecott Tunnel.

16           DR. WITSCHI: There's a light at the end of it.

17           CHAIRMAN FROINES: I think your implication was  
18 that the light will seem very far away, though.

19           DR. WITSCHI: Well, you don't know if it's a light  
20 or a train coming there.

21           DR. GLANTZ: Could I -- so the chairman thinks we  
22 deserve a raise, I think.

23           CHAIRMAN FROINES: No. I'm not saying that.

24           DR. GLANTZ: No, I know --

25           CHAIRMAN FROINES: I do think that it raises a

1 question, for example, Elinor Fanning has played a very  
2 important role as a consultant to this panel, and so I think  
3 that we have to consider how can we best do our job within  
4 the time constraints that everybody on the panel has.  
5 That's all I'm raising.

6 DR. GLANTZ: Can I just get back and add, I  
7 actually agree with that. And I think she's done a great  
8 job, actually. That summary, which I reread, which you sent  
9 around to us with bad memories, was very excellent actually.

10 I just want to clarify a couple of points.

11 One, what you're doing is you're going back over  
12 the existing list and looking for areas in which kids have  
13 special susceptibilities; is that right?

14 DR. MARTY: Yes.

15 DR. GLANTZ: So if the kids are sort of like  
16 everybody else, or we already -- in a few cases, as you  
17 mentioned, already looked at kids, and that in the report  
18 that was done, those don't have to be revisited?

19 DR. MARTY: Exactly.

20 DR. GLANTZ: So this is just looking for places  
21 where they may have been overlooked?

22 DR. MARTY: Right. For the vast majority of  
23 toxics, we're not going to have information specific to  
24 kids. We might have for a handful some information where  
25 they exposed animals young or even in utero, and we actually



1 if it's a developmental endpoint for a reference exposure  
2 level, we've actually already looked at the developmental  
3 endpoints.

4 So the bigger issue is our general, in my mind,  
5 are our general methodologies adequate to protect kids. For  
6 example, we have the tenfold uncertainty factor intraspecies  
7 variability, is that adequate to protect a kid versus an  
8 adult?

9 So those are the kinds of questions that we're  
10 going to address when we look at our risk assessment  
11 methodologies.

12 CHAIRMAN FROINES: But you also have to look at  
13 mechanistic issues, because if you know that certain enzyme  
14 systems develop slowly and certain chemicals require  
15 biotransformation to be activated, then you have a potential  
16 enhanced risk because of the pace at which developmental  
17 processes occur.

18 DR. MARTY: Correct.

19 It also works in the other direction, where a  
20 chemical has to be activated. There's a very nice article  
21 by Cristay, Tia Cristay, and he looked at the development of  
22 cytochrome P 450 isoforms starting mid-gestation through age  
23 25.

24 And you can clearly see that the isoforms are  
25 different neonatally and develop slowly into adults, and in

1 many cases in the pharmaceutical literature you can see that  
2 kids can't activate a chemical to a proximate toxicant.  
3 Likewise they can't detoxify either, if that's the step  
4 that's --

5 CHAIRMAN FROINES: We're going to have to work out  
6 a way in which some of the important articles that you  
7 identify end up getting sent to the panel, so that our level  
8 of knowledge can grow with yours, because a lot of people  
9 don't necessarily work on some of these.

10 DR. MARTY: I'd be happy to set up some  
11 presentations to the panel too, prior to you getting the  
12 document for review, that go over some of these main issues.

13 CHAIRMAN FROINES: I think, keep in mind with  
14 Peter's request is that he would like to see the 90 and the  
15 30 and the, you know, whenever you can release that I think  
16 people would be interested to see how the process is going  
17 forward.

18 DR. GLANTZ: My understanding was that we should  
19 be able to look at that stuff prior to public release. I  
20 mean, we're certainly in the reports that have been  
21 developed, we've seen prerelease drafts.

22 DR. MARTY: Yes.

23 DR. GLANTZ: And I actually had the same thought.  
24 I kind of like to see what the lists were too.

25 So I think it would be helpful if those could be

1     circulated.

2             The other thing, and I'm not trying to make more  
3     work for you when you've already got a lot of work, but you  
4     may have already done this, if you had it, it would be  
5     interesting to see which things on the list have sort of  
6     already been taken care of for the reasons that you outlined  
7     before. I think that would be a useful thing to just know.

8             DR. MARTY: Okay.

9             DR. GLANTZ: There may be a few.

10            DR. MARTY: Why don't I put together a packet for  
11     the panel then and send it to -- describes what we've  
12     already done and where our thoughts have been on this issue.

13            DR. FUCALORO: Because it's not clear to me  
14     exactly how you get this list down, and I think that's what  
15     Peter is saying, and I'd like to see --

16            CHAIRMAN FROINES: There's all this data that's  
17     developing on children being born, and I don't remember the  
18     details very well, low birth weight or obese or various  
19     things, that then make them susceptible to hypertension  
20     later in life, to cardiovascular disease, and one of the  
21     questions that we really have no knowledge of is to what  
22     degree do environmental chemicals impact that process as  
23     they go through their maturation, given that they start with  
24     certain characteristics that put them at risk.

25            And I don't know if there's any literature

1    whatsoever on that.

2               DR. MARTY:  There's some literature.  For example,  
3   Ira Taeger and John Baums and Kent Pinkerton and others have  
4   looked at lung development and they actually have some  
5   studies where they looked at impacts of prototype toxins on  
6   lung development and how that affected lung function later  
7   on.

8               There are some human studies that have been done.

9               A lot of people have focused on premature births  
10  and how that impacts function later on.

11              But there are studies that have looked at toxicant  
12  exposure and how that impacts function later on.

13              So there is a certain amount of literature that  
14  we're looking at.

15              DR. FRIEDMAN:  I don't know if this is premature  
16  to ask, but just to get a feel for your thinking, I'm just  
17  thinking of two hypothetical toxic air contaminants, one of  
18  which would cause a rash in a child, but not in an adult.  
19  Say one out of every hundred children exposed to it would  
20  get a rash, but adults are not affected for some reason.  
21  Whereas another chemical would cause both the children and  
22  adults to get, say, one in 10,000 exposed would get  
23  leukemia.  Which would you say is the more important?

24              DR. MARTY:  It's hard to answer that question, but  
25  I can assure you that one of the things we're looking at is

1 not just a quantitative difference in response, but a  
2 qualitative difference in response.

3 And the one thing that pops into my mind, which  
4 everybody is familiar with, is Minamata disease. You had  
5 moms exposed to the same amount of methyl mercury within a  
6 bounds, as the babies either in utero or just post-natally,  
7 and it's the babies that had profound neurologic impacts and  
8 the moms had nothing measurable.

9 So that's an example of both a qualitative and  
10 quantitative. You couldn't even measure the effect in an  
11 adult.

12 And we see that a lot in development studies  
13 where --

14 DR. FRIEDMAN: I'd be much more worried about  
15 something that causes leukemia in one out of every 10,000  
16 kids exposed to it, even though they're not more susceptible  
17 than adults, than I would in something that causes a  
18 transient skin rash in one out of a hundred, even though  
19 adults don't get it at all.

20 DR. MARTY: Yeah. Oh, yeah, most definitely. So  
21 the severity of effect, that's something that considered.

22 DR. FRIEDMAN: That will definitely enter into --

23 DR. MARTY: Yes.

24 CHAIRMAN FROINES: Question about one of the  
25 things that triggered concerns about children, of course,

1 was the -- I think it was a 1993 National Academy of  
2 Sciences report on pesticides in children, and the question  
3 is where do pesticides fit into this equation and is there  
4 any relationship with DPR within that context.

5 DR. MARTY: Right now the statute only addresses  
6 already identified TACs. So insofar as there are pesticides  
7 that are identified as TACs, they're subject to this whole  
8 process.

9 DPR has talked to me about what we're going to do  
10 with kids. We're trying to get everybody included,  
11 especially when we start looking at our risk assessment  
12 methodologies and revising those, because they are well  
13 aware that that's going to impact them as well.

14 DR. GLANTZ: Now, what happens if something gets  
15 added as a TAC, does that just automatically get rolled into  
16 this process?

17 DR. MARTY: It's rolled right in and in fact if  
18 there's a candidate TAC from the get-go we're going to be  
19 looking at whether or not there's differential impacts on  
20 children.

21 CHAIRMAN FROINES: So if we were to get styrene  
22 for just as an example, and I think we are going to get  
23 styrene -- I'm looking at Janette Brooks.

24 FROM THE AUDIENCE: It's already a toxic air  
25 contaminant.

1           CHAIRMAN FROINES: But I thought we were still  
2 going to get it.

3           My point is that I guess this is the same question  
4 as Stan, will every TAC hence forth have a section that  
5 deals with children's susceptibility?

6           DR. MARTY: Yes. Yes.

7           CHAIRMAN FROINES: So that's an ongoing  
8 requirement forever?

9           DR. MARTY: Yes.

10          DR. GLANTZ: Well, you know, this brings up the  
11 issue of ETS, which we took right up -- I can't resist this.  
12 We took right up to the point of recommending listing as a  
13 TAC, and there are huge differential effects on kids. Huge  
14 huge differential effects on kids, and they are the most  
15 susceptible subpopulation.

16          And it seems to me that we ought to finish the  
17 process that we started with ETS, and it ought to be rolled  
18 into this, because it's just the elephant sitting in the  
19 middle of the room, you know, when you talk about effects of  
20 air toxics on children.

21          I don't know how the rest of the panel feels about  
22 that.

23          DR. WITSCHI: I would say that's the most  
24 important one there is.

25          DR. GLANTZ: How can we get the process, you know,

1 we took it right up to the end, and I think all that's left  
2 to be done, and I don't know what's involved, would be for  
3 the ARB to list it. And I mean is there anybody here who  
4 could speak to that?

5 CHAIRMAN FROINES: First time Janette's opened her  
6 book all morning, to write something down. It was, is now.  
7 So that she may be making a note --

8 FROM THE AUDIENCE: I'm being watched.

9 CHAIRMAN FROINES: I actually have no idea whether  
10 you opened your book earlier but --

11 DR. FUCALORO: It was a good guess.

12 DR. GLANTZ: That's why you're the chair.

13 I mean, I think that -- I mean, with what  
14 Dr. Witschi said, I mean, I think we should -- we're just  
15 about there with that. It got sort of put aside largely  
16 because of political pressures at the time and I think we  
17 ought to just finish it and it ought to be part of this  
18 process. The basic work is all done, including there's a  
19 whole chapter too on kids in the report.

20 DR. WITSCHI: I'm not so sure it was the political  
21 pressures. I thought one of the reasons was that it's  
22 unenforceable.

23 DR. GLANTZ: No, I think it was political pressure  
24 from the Governor's office. I was told that in those words  
25 by several sources. But we have a new Governor now.



1           CHAIRMAN FROINES:  So this is an action item.  
2   This is an action item, and so I think that the action item  
3   would be that the panel request consideration from ARB about  
4   taking up ETS, and that that would imply that the panel is  
5   suggesting that ARB take up the ETS.

6           DR. FRIEDMAN:  I just didn't realize that there  
7   was this -- that process didn't get completed because we got  
8   this big book, beautiful report.  I thought it was all done.

9           Could you just for the record tell us what  
10  happened?  I didn't know that it wasn't a toxic air  
11  contaminant.

12          DR. GLANTZ:  What happened is -- were you at the  
13  meeting?  I forget who was at the ARB meeting.

14          What happened was there was a huge amount of  
15  political pressure put on by the Governor's office, and as a  
16  result the ARB, I forget technically what they did, maybe  
17  someone can -- Bill Lockett maybe can tell us.

18          I think they took notice of it or received it, but  
19  they didn't act to list it.

20          And in fact one of the members, there was a  
21  Dr. Friedman, I think, also on the ARB and he said why  
22  aren't we listing this, and there was some mumbo jumbo  
23  response provided.

24          And I sat quietly because at the time we were  
25  embroiled in the controversy over diesel and I thought --

1 but I think now is just time to go back to them and say you  
2 have a perfectly good report. It went through the whole  
3 process. There was all the public comment, et cetera,  
4 et cetera.

5 The only thing that's changed since then is the  
6 evidence has gotten stronger and we should ask them to  
7 simply do what -- finish the process, whatever that, I don't  
8 know exactly what would be involved.

9 And then I think we should ask them to do that  
10 expeditiously, and I think it should be rolled into this,  
11 what's the bill?

12 DR. FUCALORO: Stan, when you say we should ask  
13 them --

14 DR. GLANTZ: The SRP. I think the SRP should  
15 request --

16 DR. FUCALORO: Should actually do something?  
17 That's not generally with our purview. I don't mind doing  
18 it, I'm just saying let's understand -- what we do is -- we  
19 did our job.

20 DR. GLANTZ: Yeah.

21 DR. FUCALORO: We had the findings on it.

22 And I was like you, Gary, I didn't realize --

23 DR. GLANTZ: Yeah. Well, there was -- I think we  
24 should -- I don't think we can direct them to do anything,  
25 but I think we should request that they take it up

1 expeditiously.

2           And then once that's done, that it be rolled into  
3 this process Melanie is talking about.

4           CHAIRMAN FROINES: Well, I think Tony is raising  
5 an important point, because without going into all the  
6 detail, the two suits that have been brought against the  
7 panel allege that our -- let's take diesel, that our unit  
8 risk factor is a regulation and agencies are using it as a  
9 regulation.

10           Now, we never intended it that that be the case,  
11 but that's what's being alleged.

12           And there has always been a very important  
13 historical separation philosophically, intellectually  
14 between the risk assessment process and the risk management  
15 process and that we have stayed out of the risk management  
16 process to preserve the scientific integrity of the panel.

17           And I think the two that agree that we start to  
18 make a recommendation about a process that in essence sets  
19 in motion a regulatory process, and then we have, although  
20 we do recommend compounds be listed as toxic air  
21 contaminants.

22           So on the one hand we recommend they be listed as  
23 toxic air contaminants and so it seems to me that that's  
24 what we should do at this point, because that's within our  
25 historical purview.

1           If we went beyond that in any way to recommend  
2   that all of sudden now ARB should start to regulate ETS,  
3   then I think that's dangerous.

4           DR. GLANTZ:  No, no.  I agree.  I was not  
5   proposing that we recommend that they regulate anything.

6           But I think it may be that the appropriate thing  
7   to do would be to go back and get the findings, because  
8   there was a lot of negotiating about that wording, because  
9   of this issue, and simply move forward a recommendation that  
10  it be listed as toxic air contaminant, which isn't, I think  
11  isn't exactly -- I think the findings sort of side stepped  
12  that issue, because of all the politics, and so it may be  
13  that that's all we should do is just recommend that this  
14  list this.

15          DR. FUCALORO:  I'd like to see our document again.  
16  I don't have a copy.

17          DR. GLANTZ:  I can run upstairs to get it.

18          DR. WITSCHI:  I personally -- I was given those  
19  final list of compounds and ETS wasn't one of them.  It just  
20  was lost, because the most important public health problem  
21  would not be there.

22          And I think it's the panel's, I wouldn't say  
23  obligation, but we can certainly point this out.

24          CHAIRMAN FROINES:  Bill, do you have any -- Bill  
25  or Janette, and I don't know who is the most appropriate,

1 but Bill was involved in this historically. If we go back  
2 and look at our findings --

3 DR. GLANTZ: I notice he's staying back in the  
4 back.

5 CHAIRMAN FROINES: I notice that. I wasn't going  
6 to comment.

7 MR. LOCKETT: My apologies, Mr. Chairman.

8 DR. FUCALORO: State your name and position,  
9 please.

10 MR. LOCKETT: Bill Lockett with the Air Resources  
11 Board.

12 I've only heard portions of this discussion, so  
13 I'm happy to respond.

14 CHAIRMAN FROINES: I think that the question that  
15 Stan is raising is, and I don't even know if we need an  
16 answer from you, I think it's really up to the panel. I  
17 think that if you have any clarifying comments, I think that  
18 would be what we would seek.

19 I think what Stan is suggesting is that we take  
20 the findings that we developed on ETS, review them and  
21 perhaps send a new version, if you will, that recommends  
22 that ETS be listed as a toxic air contaminant.

23 MR. LOCKETT: I gather from that you're thinking  
24 about updating the findings that the panel did before?

25 CHAIRMAN FROINES: That's right. I think that's

1 right. Does everybody agree?

2 DR. GLANTZ: Well, there's two things you could  
3 do. You could update them, which would require collecting,  
4 probably going through and adding to the literature. And  
5 what that would do, because it's the literature I follow, is  
6 it would further strengthen them.

7 Or what I was just thinking of is to just take the  
8 findings as they existed, and given that I don't think  
9 anything has come forward that would lead us to -- lead to  
10 less strong findings, and simply forward those to the board  
11 and say we recommend this be listed as a toxic air  
12 contaminant. Probably we could --

13 DR. FUCALORO: Do the findings say that?

14 DR. GLANTZ: Maybe what we should do in the  
15 interest of time is table this discussion, and at lunch I  
16 can go get that stuff out of my office or we can look.

17 But I think the clear intent of my suggestion is  
18 that we -- that the board, that we do what we can to get the  
19 Air Resources Board to finish the process of listing ETS as  
20 a toxic air contaminant, which didn't happen when it was  
21 presented to the panel -- or to the board, rather.

22 CHAIRMAN FROINES: I think that the way to say --  
23 let me just say it a little differently. I think because I  
24 am concerned about the risk assessment, risk management  
25 process, and I think that what we can say is that based on

1 new scientific evidence has accumulated, and, secondly,  
2 based on the concern with children's health that we think  
3 the panel would like to review its recommendations with  
4 respect to recommending ETS as a toxic air contaminant,  
5 period. And send any augmented findings that we consider  
6 relevant.

7 DR. GLANTZ: The one thing I would add to that, I  
8 mean, I think that we probably shouldn't -- we probably  
9 can't act on that at this meeting, because it's not on the  
10 agenda, but I would hope that we could do this  
11 expeditiously, given the deadlines that are established in  
12 the bill that Melanie was talking -- was it SB 25 -- in SB  
13 25, so that this can be taken into account in those  
14 deliberations, which are operating on a pretty short time  
15 frame.

16 CHAIRMAN FROINES: It's particularly interesting,  
17 because, as I said earlier, there's a lot of work coming out  
18 now on polymorphisms, genetic polymorphisms, in relation to  
19 ETS, and so there's a very strong database, very  
20 sophisticated database emerging with respect to ETS.

21 DR. GLANTZ: You know, the other thing, and then I  
22 think we should probably move on, but one of the areas  
23 that's gotten very hot lately is the issue of breast cancer,  
24 ETS and breast cancer, and it's beginning to look like  
25 exposures during puberty are particularly important.

1           So this is an area where another very important  
2   endpoint that may -- I mean, it's looking like there aren't  
3   big effects in older women, but in women during puberty and  
4   first pregnancy, that exposure seems to be the riskiest.

5           So I mean I think it's very -- that isn't in the  
6   document that we approved, because that research was, I  
7   think, was published after it was written, but I think it's  
8   very important that that get into these SB 25 discussions.

9           DR. MARTY: That's primarily studies with active  
10   smokers?

11          DR. GLANTZ: No, no. Passive smokers.

12          CHAIRMAN FROINES: Does the panel have any other  
13   comments about the SB 25 discussion?

14          Thank you, Melanie.

15          Let's take a ten-minute break and then go on.

16          (Thereupon a short recess was taken.)

17          CHAIRMAN FROINES: We're going to go to the  
18   follow-up discussion, item 4, follow-up discussion of the  
19   October 4th panel workshop.

20          Because that's going to be a progress report,  
21   rather than them coming in with firm risk assessment  
22   guidelines for our consideration, and I thought that since  
23   it is an updating about their activities since they -- since  
24   the workshop, that that again was something that we could do  
25   without Paul being here.



1           So Gary is back, so we do have a quorum.

2           So we are going to move on to item 4, and it  
3 appears as though Melanie and Paul Gosselin are going to be  
4 the participants.

5           DR. FUCALORO: Or two victims.

6           MR. GOSSELIN: I wouldn't say that.

7           Thank you.

8           At the last meeting's workshop on OPs, we left  
9 that workshop and went back to go back and take a look at  
10 our OP, the policy we have for OPs, and one of the things in  
11 consultation with OEHHA to come back and present to the  
12 panel what our policy guidelines are regarding OPs, and we  
13 have, as you know, a number of OPs that have already come  
14 before the panel and we have a number of them coming up, and  
15 we wanted to make sure that the criteria we used and the  
16 issues are well articulated, and we have a standard process  
17 of dealing with them.

18           When we went back and looked at some of the draft  
19 papers that we've been using over the years, and I think in  
20 light of the lengthy discussion over how EPA went through  
21 and crafted their policy, we actually -- and OEHHA came  
22 across the same lines, that there needed to be a, I think, a  
23 major rewrite and almost a new document that would much more  
24 clearly articulate, without any vagueness, what sort of  
25 issues we deal with with risk assessment and OPs and to try

1 to clarify how we view some of those scientific issues.

2           What we wanted to do today, and staff has spent  
3 the last couple weeks spending a considerable amount of time  
4 working through these issues that have come to the point, at  
5 least today, is a status of the outline and presentation of  
6 some of the issues that will go into the policy. It's going  
7 to take some more time to actually go through some of those  
8 issues and put pen to paper and make sure they're  
9 articulated in a way that it's far more definitive and clear  
10 than some other policies that are out there.

11           At this point I'll turn it over to Melanie to give  
12 the progress to date on this, and what you'll also find is  
13 we're going to have a staff joint presentation.

14           CHAIRMAN FROINES: Paul, just before we move  
15 ahead, when do you anticipate that you would be coming back  
16 to the panel with the final document for review?

17           MR. GOSSELIN: We're actually considering a status  
18 in January, but some of the issues, as we heard in the  
19 workshop, are fairly detailed and complex, so I would say  
20 five, five, six months.

21           CHAIRMAN FROINES: Five or six months?

22           MR. GOSSELIN: I think one of the things that as  
23 staff started to take a look at this, we wanted to make  
24 sure -- and that was kind of the point from the workshop, to  
25 make sure that what guidelines and policies we come out with

1 are going to be fairly solid, that it's not going to be  
2 vague, and articulate some of the points you'll hear in a  
3 moment.

4 We're trying to expedite this as quickly as  
5 possible and maybe get it done sooner than that, but I think  
6 in January we'll have a better idea on the status.

7 CHAIRMAN FROINES: Why don't we -- let's assume  
8 six months from the time of the workshop, so that workshop  
9 was held, what was the date? October. So if you figure  
10 November, December, January, February, March, so you  
11 would -- so shoot for a final document in at an April  
12 meeting.

13 Is everybody comfortable with that?

14 That wasn't just a question to the panel, and I  
15 heard some comments in the back of the room there.

16 DR. GLANTZ: I'm comfortable. I think that would  
17 be quite reasonable. I mean, we do want to move this along.

18 DR. FUCALORO: On the other hand, we don't want to  
19 push too hard. That's why we're asking. So I guess your  
20 response --

21 DR. GLANTZ: I think six months from the workshop  
22 is reasonable.

23 DR. FUCALORO: I guess I'm looking for a response  
24 from staff.

25 DR. GLANTZ: I want to push. Six months after the

1 workshop. I was expecting something back in a month or two.

2 MR. GOSSELIN: Well, we can give you item number  
3 4, question 3. And honestly I think it is -- I'll have to  
4 go back and talk to staff about exactly what, because some  
5 of these issues are complicated.

6 And I think you heard a lot of groans about the  
7 six-month time frame on getting this together, and they have  
8 spent the last couple of weeks looking at these issues  
9 critically, and wanting to get a policy that when it comes  
10 back here we're not going to exchange a lot of questions and  
11 have us sit here and say, well, we really don't know, or  
12 it's a case-by-case basis, and get into a real vague  
13 exchange.

14 What I could do is go back after this, confer with  
15 staff and get a better time line at the next meeting as to  
16 exactly how soon a draft can be put together.

17 CHAIRMAN FROINES: All right. I don't know if  
18 anybody else wants to comment, but the comment about fair  
19 amount of effort in the past couple of weeks, remember, it  
20 has been seven weeks since the workshop, so the danger is  
21 that these things -- if the endpoint becomes very open  
22 ended, people treat it like a gas, it fills any volume you  
23 give it, you know. And we want to avoid that at some level.

24 So I think Stan is right to push, but I think you  
25 have to push and make it also -- make it reasonable so we

1 get the best product possible.

2 It also means that the panel has this also, and  
3 one of the points is that --

4 DR. GLANTZ: What did you hold up there?

5 CHAIRMAN FROINES: This is the transcript plus all  
6 the overheads.

7 DR. GLANTZ: That's the stuff that came in that  
8 binder.

9 CHAIRMAN FROINES: That came with the workshop.

10 So the panel needs a certain amount of time to  
11 review this as well.

12 But so I would still argue that an April date  
13 would be good, but then the burden then becomes on you to  
14 tell us why that can't be met.

15 Because we are developing a risk assessment  
16 guideline document. We're not doing the science. We're  
17 doing the interpretation of the science.

18 DR. GLANTZ: Just for my information, when you  
19 held up the material from the workshop and said review it,  
20 you just meant review that for our edification. There's no  
21 action item in there, is there?

22 CHAIRMAN FROINES: Well, yeah, because they're  
23 going to be coming with presumably a relatively  
24 sophisticated document when they actually make their final  
25 presentation, so we just want to make sure -- there was a

1 lot of really good information at that workshop.

2 DR. GLANTZ: Right. But, again, there's nothing  
3 in the workshop training materials that are action items for  
4 us. That's for our -- that's to educate us.

5 CHAIRMAN FROINES: Yeah.

6 DR. GLANTZ: I just wanted to be sure I didn't  
7 miss something.

8 CHAIRMAN FROINES: Is everybody comfortable with  
9 where we are?

10 Tony?

11 DR. FUCALORO: Yeah.

12 DR. MARTY: This is Melanie Marty from OEHHA. I'm  
13 acting as George Alexeeff today because he could not be here  
14 today.

15 I have a little slide -- Laurie, could you move  
16 that down just a little bit.

17 This just describes the progress to date on coming  
18 up with a policy on cholinesterase inhibition and the use of  
19 that type of data.

20 CHAIRMAN FROINES: I'm sorry. There is one more  
21 question that relates to this.

22 For example, we have azinphos methyl before us at  
23 this point, and between now and April do you anticipate any  
24 other OPs coming before this panel? Because obviously we  
25 have a chicken-egg problem. If you've got a risk assessment

1 process that you're working through, but you're sending  
2 documents to us, we want to ensure that the documents that  
3 come to us have the most up-to-date policy with respect to  
4 risk assessment.

5 MR. GOSSELIN: Yeah.

6 CHAIRMAN FROINES: I don't want to review azinphos  
7 methyl and then three months from now go back and have to  
8 re-review it again.

9 MR. GOSSELIN: Yeah. And I don't think we want to  
10 do that either, but we have had OPs that have come through  
11 the panel. We have azinphos and potentially chlorpyrifos  
12 that might come before the panel in April.

13 I think as -- I think what I would like to seek to  
14 try, because I wouldn't like to see all the documents be  
15 totally ground to a halt, but I think there needs to be some  
16 understanding that the documents that whether it's azinphos  
17 or chlorpyrifos, are done in concert with the development of  
  
18 the guidance, that shouldn't be any different than the  
19 issues that were raised and discussed on the previous OPs  
20 that went through.

21 So I don't think the issues are going to be  
22 totally unrelated, but in the end it should be consistent  
23 with what that policy document looks like.

24 CHAIRMAN FROINES: We just don't want to have to  
25 do too many bites on the apple.

1           MR. GOSSELIN: No. I agree, but I think probably  
2     proceeding with those documents going forward, but keeping  
3     one foot in a real conscious effort as to where this other  
4     process is going, so we're not too far off.

5           CHAIRMAN FROINES: Okay. Go ahead.

6           DR. FUCALORO: The apple may have very many  
7     organophosphates on it. We want to minimize those bites on  
8     those apples.

9           DR. MARTY: Okay. I just have one slide on our  
10    progress to date.

11           In looking at data on cholinesterase inhibition  
12    and how to use that to assess health impacts, staff are  
13    reviewing current policies, slash, thoughts. Some of these  
14    are really informal policies or proposed positions,  
15    including the US EPA dated the year 2000, which you heard  
16    about at the workshop, CDPR's policy that was dated 1997,  
17    we're reviewing that.

18           Also the UN's, FAO and World Health Organization  
19    had a paper, a formal paper in 1998 on pesticides in food  
20    where they have a section on the use of cholinesterase  
21    inhibition data.

22           And we're also evaluating a 1999 position paper  
23    from an industry panel that states their position on the use  
24    of cholinesterase inhibition data.

25           We conducted really a preliminary literature



1 review updating the literature, particularly since CDPR did  
2 their 1997 document, and what is new out there with regard  
3 to cholinesterase inhibition and types of data and  
4 conclusions you can make from that.

5 We've had a planning meeting between OEHHA and  
6 DPR, and we have agreed to collaborate to get work together  
7 to establish a common policy on cholinesterase inhibition  
8 and use of that data, both in public health risk assessment  
9 and in more general context.

10 In the presentation that you'll be hearing from  
11 staff will cover issues, goals and our future work plan.

12 So now if we can have staff from OEHHA, Keith  
13 Pfeifer from DPR, and Bob Howd from OEHHA, will provide you  
14 with some more information.

15 CHAIRMAN FROINES: Presumably that policy will  
16 attempt also to include children's considerations as well?

17 DR. MARTY: Yes.

18 DR. PFEIFER: Good morning. My name is Keith  
19 Pfeifer. I'm one of the senior toxicologists with the  
20 Department of Pesticide Regulation and today

21 Dr. Howd and I are going to share in the initial  
22 presentation of the panel, and primarily we're going to be  
23 looking at some of the key issues in the interpretation of  
24 cholinesterase inhibition.

25 And I just wanted to make the point up front here,

1 that because the organophosphates and carbamates primarily  
2 act through this mechanism, this is why we're initially  
3 looking at cholinesterase.

4 However, we will not ignore any other systemic  
5 toxic effects and certainly also focus in on developmental  
6 effects.

7 What we tried to do is phrase some of the issues  
8 in the forms of questions.

9 So the first question, what are the physiological  
10 functions and toxicological significance of cholinesterases.  
11 And primarily here we're interested in the  
12 acetylcholinesterase and butyrylcholinesterase, sometimes  
13 call pseudocholinesterase.

14 However, there are other esterases that interact  
15 with organophosphate compounds.

16 But again we're primarily interested in these two,  
17 since these two are the ones that are most commonly measured  
18 and looked at for toxicological significance.

19 The tissues that are generally looked at for these  
20 cholinesterases are the brain, in some cases peripheral  
21 tissues, commonly erythrocyte and commonly also in plasma  
22 and/or whole blood.

23 The reason that we put up with the brain, the  
24 whole versus regions, is that occasionally we've reviewed  
25 studies where there is some differential or preferential

1 inhibition depending on which region of the brain is  
2 sampled, and this may be due to differential metabolism or  
3 binding site, so that raises a question as to whether whole  
4 brain or specific critical regions of the brain might be  
5 more appropriate.

6 With regard to peripheral, and we have the  
7 diaphragm there as an important organ that can be regulated  
8 by acetylcholinesterase, EPA recently has suggested that as  
9 part of their general protocol, that peripheral  
10 cholinesterase be routinely sampled to get an idea of impact  
11 on organ effects. So this is one reason that that's up  
12 there.

13 Occasionally you'll hear that measurements of  
14 erythrocyte or RBC acetylcholinesterase may serve as a  
15 surrogate with that regard.

16 And this isn't just for the diaphragm. It might  
17 be a heart, spleen or skeletal muscle also.

18 Again, moving down to enzyme speciation, we're  
19 primarily talking about acetylcholinesterase and  
20 butyrylcholinesterase. And butyrylcholinesterase is found  
21 in the central nervous system and in other tissues.

22 However, a clear function for this enzyme has not  
23 always been clearly delineated. There is some evidence that  
24 it may be important in certain drug metabolism and certainly  
25 some evidence that it may be important in the early

1 development of the nervous system.

2 Butyrylcholinesterase is a predominant form of  
3 cholinesterase in human plasma, and on the next slide I'll  
4 be contrasting that with some of the rat information that we  
5 have.

6 Acetylcholinesterase, the function is well  
7 characterized, both in the central and in the peripheral  
8 nervous system both.

9 And also there's some recent evidence of  
10 acetylcholinesterase in lymphocytes, which may imply a  
11 certain immune function, and erythrocytes, red blood cells,  
12 the predominant form is acetylcholinesterase, but again the  
13 function not clearly delineated.

14 The second question we phrased is what is the  
15 extent of intra and interspecies variability.

16 Now, under intra we're primarily concerned about  
17 the variability in humans. With regard to gender, for  
18 example, males usually have higher plasma cholinesterase  
19 level. With regard to age, there is evidence in neonatal  
20 rats that they have lower cholinesterase activity, thereby  
21 maybe rendering them potentially more susceptible to  
22 organophosphate compound.

23 And again the area of enzyme polymorphism, for  
24 example, there are five known genotypes for plasma  
25 cholinesterase in humans.

1           In the area of interspecies variability, again  
2   primarily comparing laboratory animals with humans, one area  
3   that's interesting is the ratio of acetylcholinesterase to  
4   butyrylcholinesterase.

5           In the human plasma, the ratio is one to a  
6   thousand.

7           In rat plasma, female rat plasma, the ratio is one  
8   to two.

9           In the male rat plasma the ratio is three to one.

10          So we have some normal type of variability already  
11   in these values.

12          Also, as far as interspecies differences, looking  
13   at anatomical differences, such as the blood brain and  
14   placental membranes.

15          And I guess the bottom line question comes out as  
16   to what would be the appropriate default uncertainty factors  
17   to consider under both inter and intraspecies variability.

18          Another question that we pose is how are structure  
19   activity relationships useful in looking at cholinesterase  
20   inhibitors.

21          And maybe rephrasing this, are there other factors  
22   or any factors that can help characterize the  
23   pharmacokinetics and subsequent correlations between  
24   cholinesterase inhibition and clinical signs.

25          As far as a physical chemical property, one

1 example is octanol water partition coefficient, which  
2 generally is an indicator of the ability of a chemical to  
3 partition more into lipid soluble compartment or in some  
4 cases the ability to cross, say, the blood-brain barrier.

5           Structure activity might be useful in grouping of  
6 organophosphates with possible correlations. You could use  
7 the ring structures, the phenyl, heterocyclic or aliphatic,  
8 or you can get into more detailed areas, grouping them into  
9 the moieties that are on the site change. Some of the  
10 examples are on this slide.

11           Certainly, structure activity relationships give  
12 you some idea of differences in biotransformation, both  
13 activation potential and potential detoxification  
14 characteristics.

15           And then also primarily in vitro you can have  
16 different binding affinities to characterize these  
17 inhibitors.

18           The area of laboratory variability in the  
19 measurement of cholinesterase inhibition, as you know, is a  
20 favorite topic of Dr. Barry Wilson. And I think it is an  
21 important area that is sometimes overlooked, and I think  
22 it's something that should be at least considered and  
23 addressed in any policy development for how to interpret  
24 cholinesterase inhibition.

25           Certainly, you want uniform sampling and handling

1 of both tissues, and with humans and blood and plasma  
2 sampling he'd like to see standardization of methodology. I  
3 know Dr. Wilson is a proponent of that.

4 And even so, with standardization of methodologies  
5 you still can have intra and a great deal of inter  
6 laboratory variability.

7 Both Dr. Wilson and Dr. Padilla several years ago  
8 did a study, a published study, where several laboratories  
9 measured cholinesterase inhibition using a standard  
10 methodology, and they still came up with variability in the  
11 double digit percent area.

12 So this leads to the final point up there, what is  
13 the impact of this type of variability on the interpretation  
14 of cholinesterase inhibition, and a more pointed question  
15 might be is cholinesterase inhibition below a specific  
16 percent within the variability of an analytical method and  
17 what would be the toxicological significance then of that.

18 With that, I'll turn the rest over to Dr. Howd.

19 DR. HOWD: I'm Bob Howd of the Pesticide and  
20 Environmental Toxicology Section of OEHHA, and have worked  
21 in that context with DPR over a number of years on  
22 interpretation of cholinesterase inhibition data and other  
23 kinds of data for pesticides.

24 When we start to develop a consistent methodology  
25 for pesticides, we have to think about dose response

1 assessment for the cholinesterase inhibitors, and among  
2 those things the endpoint selection is very important,  
3 because sometimes, although we think of these chemicals as  
4 cholinesterase inhibitors, cholinesterase inhibition, per  
5 se, is not the endpoint of most sensitivities. So we have  
6 to agree on when it is or is not the endpoint that we should  
7 be considering.

8 A neurological endpoint, for example, would be a  
9 good endpoint, but often the neurological tests that are  
10 available for cholinesterase inhibitors are very poor.

11 So this is one of the items in which there are not  
12 good guidelines in how you develop or select what you're  
13 going to use for the critical factor.

14 In short-term versus long-term exposures, it  
15 meshes with the next point there on tolerance that when you  
16 get tolerance to the chemicals that are as significant as we  
17 have for cholinesterase inhibitors, you have to try to  
18 figure out how you're going to evaluate cholinesterase  
19 inhibition when the same level of inhibition in a long-term  
20 exposure would actually have less effect after the longer  
21 term exposure.

22 So how do you take that into consideration in  
23 interpretation of this kind of data?

24 And my opinion, some of the chronic cholinesterase  
25 inhibition data is virtually useless, and one really should



1 be looking at different kind of exposure for those different  
2 kinds of endpoints for that kind of data, because of the  
3 question of homeostatic mechanisms coming into play in these  
4 chemicals.

5 Also, we have to look at central versus peripheral  
6 nervous system responses, and that isn't well delineated in  
7 many of the studies coming down from the manufacturers.

8 And in that regard, have to say that the basic  
9 guidelines on how you do the studies for cholinesterase  
10 inhibitors called the FIFRA guidelines are really not very  
11 good to address many of these points that we're bringing up,  
12 and that's the basic problem with interpretation of  
13 cholinesterase data.

14 If you have to do this basic set of studies  
15 concentrating, for example, on cholinesterase inhibition and  
16 have very very little data on what the actual effect is on  
17 the animal, how are you going to produce safe estimates,  
18 estimates at safe level in humans?

19 Laurie, could you go up to the next one.

20 The benchmark dose measures are something that  
21 we've been talking about at OEHHA for quite a long while,  
22 because it can help possibly solve some of the problems with  
23 the traditional LOEL NOEL approach.

24 Cholinesterase data tends to be fairly variable,  
25 as Keith was just pointing out.

1           You can look at data across many studies at many  
2 doses and incorporate that all into a benchmark model. You  
3 can get a better estimate of the true potency for, than  
4 doing risk assessment from.

5           The interpretation of that will still probably  
6 involve an uncertainty factor, and that's one thing that we  
7 have to discuss between our groups if we're going to attempt  
8 to use that for evaluating cholinesterase inhibitors.

9           I might say in this regard that US EPA does not  
10 yet use this approach for cholinesterase inhibitor  
11 evaluation, although they've been pioneers in the use of  
12 benchmark doses. It hasn't yet been applied here.

13           So there's a lot of work that needs to be done  
14 there.

15           DR. GLANTZ: Can I just ask a question -- this is  
16 just exhibiting my ignorance again. But could you go over  
17 again the difference between the benchmark dose approach and  
18 the NOEL approach?

19           DR. HOWD: Well, with the NOEL approach, if you  
20 study a chemical at one, ten and a hundred milligram per  
21 kilogram, and so you have this differences in doses by a  
22 factor of ten, and you have zero percent inhibition in one  
23 and five percent inhibition, which is not statistically  
24 significant at ten, and 80 percent of inhibition at a  
25 hundred milligrams per kilogram, how do you interpret that

1 data.

2 You have to say that the LOEL is in that case is a  
3 hundred, and the ten is NOEL.

4 Well, if you can use that in a modeling approach  
5 to determine what is some consistent amount of inhibition  
6 that you will assume to be a benchmark, and let's call it 20  
7 percent inhibition, drawn between those points, and then do  
8 your risk assessment extrapolation from that theoretical 20  
9 percent, you have a better idea of the absolute potency of  
10 the chemical, than in that more broader base approach from  
11 that three-dose experiment.

12 DR. GLANTZ: So what you're saying in the  
13 benchmark approach is you establish some specified effect  
14 level?

15 DR. HOWD: That's correct.

16 DR. GLANTZ: And then you try to estimate --

17 DR. HOWD: So you're more consistent.

18 DR. GLANTZ: Okay. Is there any standard effect  
19 level that you use?

20 DR. HOWD: That would be one of the things that  
21 we're trying to decide on which we use -- would what we  
22 would use for this evaluation to achieve a consistent  
23 response.

24 Now, one of the reasons why I back there was  
25 groaning when the six months was date was mentioned, was

1 because one of the things that we'd like to do is actually  
2 look at enough of the data from different chemicals to know  
3 what is a value neutral approach to use.

4 If you use 20 percent, what does it do to the risk  
5 assessment. Does it imply -- and uncertainty factors. Does  
6 it mean that we're less health protective than before, more  
7 health protective than before? What actually happens if you  
8 were to evaluate data that way?

9 Maybe in order to achieve a consistent approach  
10 that we could agree on, we wouldn't even be able to use  
11 benchmark approach, and use the standard approach of NOEL  
12 LOEL in what we'd bring to the committee in April.

13 That was what the problem is with a specific  
14 deadline and trying to resolve some issues like this.

15 CHAIRMAN FROINES: I think the problem you're  
16 going to find, which you already know, is that the quality  
17 and quantity of data that you can use for the benchmark  
18 approach is very limited, and so you're going to be trying  
19 to find things that you may have trouble finding.

20 And, of course, I'd love to get into a thing about  
21 how inadequate the FIFRA guidelines are, but there's no  
22 sense doing that here and now.

23 DR. HOWD: No.

24 CHAIRMAN FROINES: But I think that -- I  
25 wouldn't -- I think given the limitations of the data for

1     doing -- and we've been through it with Melanie in terms of  
2     what the chronic and acute RELs, where the number of  
3     compounds for which the benchmark dose could be used was  
4     vanishingly small, and so one has to be careful not to try  
5     to find that which may not exist.

6             And for Stan's points, I think you understood it,  
7     but basically the benchmark dose just allows you to make the  
8     better -- use the dose response data better than the safety  
9     factor.

10            DR. HOWD: Yes. For pesticides, of course,  
11     there's more data than from any other chemicals, because of  
12     the FIFRA guidelines require a relatively large number of  
13     studies compared to other chemicals.

14            But still it is a problem with data quality and  
15     interpretation of it for all of the reasons that we have  
16     been discussing.

17            To go on here, among the things that we would wish  
18     to discuss is to whether to use a statistical significance  
19     measure versus a percent inhibition measure. That's the --  
20     that's been a hassle with regard to the use of the  
21     determination of a LOEL, would be avoided if we used a  
22     benchmark approach.

23            With regard to evaluation --

24            CHAIRMAN FROINES: I don't want -- I don't want to  
25     interrupt you a lot. I just want to make one comment.

1           It seems to me that one of the things you might do  
2 on that kind of issue is interact with the panel during the  
3 course of your deliberations, because Stan may have some  
4 ideas that you can run by him that you might save him not  
5 agreeing with you when you got here in April.

6           DR. PFEIFER: Dr. Froines, we're thinking along  
7 the same liens.

8           You were asking when we might have a final  
9 product, and that date is kind of up for discussion, I  
10 guess.

11           However, in our discussions with OEHHA we thought  
12 it would be a good idea maybe to come before the panel with  
13 periodic updates on some of the key issues, maybe not just  
14 everything, but certainly some statistical type information  
15 or approaches.

16           DR. GLANTZ: Yeah. We're also available to  
17 discuss these things with you informally too, because I mean  
18 I don't want to take time now, but I would actually have  
19 dealt with the issues you just put forward differently,  
20 because I don't think you need to require -- look at  
21 statistical significance in each dose.

22           I think you can look at the dose response  
23 relationship as part of overall, and even when you're  
24 talking about trying to establish NOEL levels, we don't need  
25 to get into that.

1 DR. HOWD: That would be a break with present  
2 practice, but I agree with you that we shouldn't make that  
3 break.

4 Anyway, that's the kind of thing that we need to  
5 discuss, and it will require some time to make the decisions  
6 on what -- how we should be going forward on this.

7 CHAIRMAN FROINES: I think that California may  
8 find itself breaking a bit with EPA and the quality -- and  
9 that discussion that went on at the workshop with the fellow  
10 from EPA suggests that there's a need to break, I think.

11 DR. HOWD: To move forward to use the methods  
12 suggested in fact by US EPA for this purpose.

13 But as you heard also from Stephanie Padilla,  
14 they're well aware of these issues and would like to have  
15 some prodding of their own regulatory organization, I would  
16 think, to move forward.

17 CHAIRMAN FROINES: I think she's terrific, and the  
18 more input you got from people like Stephanie Padilla, I  
19 think the better off we'd all be.

20 DR. HOWD: Yes.

21 DR. PFEIFER: We interact with her quite a bit on  
22 our risk assessments on organophosphates.

23 DR. HOWD: To go on here, the use of the  
24 concurrent control versus baseline values is a question  
25 often with both animal and human data where cholinesterase

1 values normally change over time a moderate amount, and  
2 given the variability of the data, there will often be many  
3 different ways to do the evaluation, and you have to  
4 consider different approaches for different kinds of data  
5 sets.

6           With a root-to-root extrapolation, issues here  
7 include the extent to which you can use different exposure  
8 assumptions of estimates of amount of inhalation uptake,  
9 estimates of amount of dermal uptake.

10           There's actually relatively poor data, for  
11 example, on dermal uptake of pesticides, and often that's  
12 the major exposure route.

13           When there's this unanswered questions about the  
14 amount of metabolism that might occur with slow absorption  
15 through the skin, for example, this is a major factor in  
16 interpretation of the data. The slower a pesticide gets  
17 into the body, also the less net effect it has for a number  
18 of pharmacokinetic and toxicodynamic reasons that have to be  
19 interpreted when you make root-to-root extrapolations. This  
20 is not a small factor.

21           What weight should be given to the human versus  
22 animal data in risk assessment is another important issue.

23           I have to bring up in that context that US EPA has  
24 vowed in certain context not to use human studies anymore,  
25 and we in the State of California tend to disagree with



1     that. We think that if you got data available, you should  
2     use it.

3             And we might want to point out the inadequacy of  
4     some of the kinds of human data that is available in a  
5     single exposure, defined condition, a study by Inveress in  
6     Scotland, which is one of the laboratories that does this,  
7     there's a real problem with overinterpreting some of those  
8     studies.

9             Clinical symptoms versus clinical signs are  
10    different. This is an important issue with regard to how  
11    you evaluate animal versus human data with subjective  
12    measures that you can get in people, which often are much  
13    more sensitive than the more objective measures in animals.

14            If you have the ability to quantify nausea as a  
  
15    symptom of a cholinesterase inhibitor in a human, whereas we  
16    can't measure that in a rat or mouse, it gives you a better  
17    perspective on what the threshold dose is. And we should  
18    use that data. We should make full use of that which we can  
19    in our interpretation of what's really going on.

20            The number of treatment groups is a big problem  
21    often with interpretation of the data.

22            The number of subject and animals per group, one  
23    of the big problems is that some of the best data is in  
24    dogs, and the FIFRA guidelines only specify that four or six  
25    dogs be used, and you have to get an effect in three out of

1 four in order to have statistical significance.

2 So often we're saying, well, but there were only  
3 one animal affected, but, you know, we shouldn't ignore  
4 that. This makes another argument for using benchmark.

5 DR. GLANTZ: FIFRA says you should only use four  
6 animals?

7 DR. PFEIFER: Generally the dose group.

8 DR. HOWD: Where it's in dogs.

9 DR. PFEIFER: Four or five.

10 DR. HOWD: Rats and mice, rabbits, guinea pigs,  
11 use greater.

12 DR. FUCALORO: For any measure?

13 DR. GLANTZ: That's crazy.

14 DR. FUCALORO: That's not a statistical pool.

15 DR. GLANTZ: You have to like having them all drop  
16 dead for it -- in fact it might not even be if they all drop  
17 dead that might not be statistically significant.

18 DR. HOWD: That's what I'm getting at.

19 DR. GLANTZ: That's crazy.

20 DR. HOWD: This is a problem.

21 Of course, in the human studies they're often low  
22 numbers of subjects also.

23 Now, the adequacy of the clinical observations is  
24 also often a problem, and again with the small number of  
25 human subjects, how do you interpret that data.

1           We want to use it, but it's problematic data.

2           So there aren't consistent guidelines on how you  
3 do the studies that would answer all the questions we have  
4 about cholinesterase inhibitors, and there aren't adequate  
5 ways on how you interpret the data once you get it.

6           That's part of the reason why you got what may  
7 have seemed like double talk from the guy from EPA in your  
8 earlier meeting. It really is a difficult question.

9           CHAIRMAN FROINES: I think the word seemed, may be  
10 a euphemism, but that's okay.

11           I think it would be useful as we go forward is to  
12 let the panel know some sort of -- that because most of us  
13 don't know what the FIFRA guidelines say, and you guys do,  
14 so as you go forward, I think it's educational when you say,  
15 well, this is what we have to live with versus what we think  
16 what should be done. In other words, the compare and  
17 contrast.

18           DR. HOWD: We can't rewrite the FIFRA guidelines.

19           CHAIRMAN FROINES: I understand. I'm just  
20 suggesting just for the panel's -- this issue just right now  
21 about the number of animals is at least worth the panel  
22 knowing about, so we understand when we're reviewing data  
23 what the limitations that we're going to come up against as  
24 we look at these documents.

25           DR. HOWD: Right. I agree.

1           And we will attempt to delineate some of those  
2 problems.

3           We want to develop uniform policies to evaluate  
4 and interpret the CHE inhibition and of course that's what  
5 you've asked us to do.

6           And uniform methodologies and defaults to  
7 interpret the data, and in this regard of course it has to  
8 be more than just the cholinesterase inhibition, per se, but  
9 the effects of cholinesterase inhibitors, which is a larger  
10 context there, because there will often be endpoints, as  
11 we've pointed out, that are not cholinesterase inhibition at  
12 all, and we have to figure out how we're going to use some  
13 of that data.

14           And the big deal with regard to the use of  
15 pseudocholinesterase has always been a kicker where how to  
16 treat that as a surrogate for other effects or not.

17           We want to prioritize the steps that we need to  
18 achieve these goals, and keep you apprised of our progress,  
19 and to the extent that we need to do that, have different  
20 problems and problem areas put together by different  
21 subgroups of people so that we can keep different parts of  
22 this moving forward and assigning tasks to OEHHA and DPR  
23 representatives, keep it moving forward, because it is such  
24 a considerable task to evaluate these different data.

25           For example, if we were to work on some benchmark

1 modeling approaches to evaluate the real data that is there  
2 to assess the strength of that, strength and weaknesses of  
3 that approach to see if we could use that for developing a  
4 uniform policy, that would be a different group as opposed  
5 to one which is evaluating some of the use of the human  
6 data, for example.

7           We also want to keep track of the policy  
8 development at US EPA. We're not saying that they will  
9 solve all of our problems for us, because actually  
10 historically speaking we have moved forward faster on many  
11 of these issues than the US EPA. In fact it's been our  
12 actions that have prodded them to move in some cases.

13           So one of the things that they have provided for  
14 us most recently is a very nice piece of software for  
15 evaluation of benchmark methods that's available free and  
16 its a wonderful statistical tool. We'd like to make use of  
17 that and anything else that they can provide, including work  
18 with Stephanie's group at US EPA, to see if she can help  
19 answer questions that need to be addressed.

20           So that's the full presentation, what we are  
21 planning to do.

22           And that was again why you had a bit of a groan.  
23 There's a lot of different problems that need to be  
24 addressed here.

25           DR. FUCALORO: Yeah. This issue comes up. It's

1 the old journalism thing, do you want it good or do you want  
2 it Tuesday. In some ways we're asking you to have it soon,  
3 but then there is also a concern that somehow that this will  
4 float off into some time indefinite, and we want a time  
5 definite, of course, obviously.

6 So I suppose we can program some times in which  
7 you report on progress, and I'm just suggesting this, and we  
8 can assess whether or not we think real progress is being  
9 made and getting to the end of this, because it seems like  
10 you've convinced me you have a very ambitious program here  
11 that you're engaged in, and that's good. And I think it  
12 would be beneficial.

13 So I'm prepared to wait a little longer, but I  
14 also take note of what other people have said to make sure  
15 that things are moving at pace, and so that's what I would  
16 suggest for this spot.

17 DR. PFEIFER: I'd just like to comment.

18 Dr. Froines mentioned earlier in the meeting today  
19 that you've been here from the beginning. And I, too, have  
20 been here from the beginning, both under SB 950 and 1807.

21 And the area of cholinesterase inhibition has been  
22 like an albatross. It's something that we know we need to  
23 address and we've tried to, but we've always fallen short of  
24 coming up with some definitive statements and policies.

25 And so over the last 15 years we've dealt with it

1 on a case-by-case basis.

2 Now, if you look at what EPA has done, I don't  
3 know if even though they have looked at it more  
4 systematically if they've come up with any better  
5 conclusions than we have so far.

6 But I can assure you that I think that this start  
7 of a more systematic approach and more unified approach, I  
8 think, is going to get us a lot farther down the road.

9 And I agree with Dr. Fucaloro that if we can come  
10 up with some milestones, some times where we can present to  
11 you our progress and get feedback and suggestions on where  
12 we're going and if we're going -- if we're addressing the  
13 most appropriate issues first, then that would be useful  
14 also.

15 CHAIRMAN FROINES: I assume the panel generally  
16 agrees with Tony's suggestion.

17 So we can -- I would suggest that where you have  
18 areas of specific interest, for example, some statistical  
19 questions, Gary Friedman and Stan Glantz might be the people  
20 to talk to, so that what you want to do is try and, yes,  
21 give us progress reports, but try and resolve certain issues  
22 outside of the scope of the meeting like this, so we're  
23 not -- so we use the time at the meetings as efficiently as  
24 possible, and get as much input as you can external to the  
25 meetings, and just as a matter of efficiency, more than

1 anything else.

2 But other than that, I think it seems like it's a  
3 great undertaking.

4 Stan.

5 DR. GLANTZ: Well, I just like -- obviously, we  
6 don't want it not done right, but I sort of think they can  
7 have it done right by Tuesday.

8 DR. FUCALORO: You're a hard man, Glantz.

9 DR. PFEIFER: You have to understand at least in  
10 my group the same people that will be working on this are  
11 the same people that are doing the risk assessments for the  
12 candidates coming through.

13 DR. GLANTZ: We're the same panel that has to deal  
14 with it. You know, I just know that -- this isn't a comment  
15 on you, but with lots of people it always gets done at the  
16 last minute, so it's just a question of when the last minute  
17 is.

18 But we're reasonable people here.

19 DR. PFEIFER: I know.

20 DR. GLANTZ: If we see progress --

21 DR. ATKINSON: We are?

22 DR. GLANTZ: Some of us are.

23 DR. FUCALORO: Where did we go wrong?

24 DR. GLANTZ: And well dressed, too.

25 CHAIRMAN FROINES: Well, but I think you've -- I



1 think one thing that might be helpful is you've raised a  
2 series of generic questions and general questions.

3 And it seems to me that the next step that you  
4 could undertake is to define specific questions that you  
5 need to answer, and then tell us what they are, and then  
6 tell us the progress with respect to the specifics, not the  
7 general questions, because then we really know whether  
8 you're making progress or not.

9 DR. HOWD: We had a set of 25 slides on the  
10 technical details that we thought would be inappropriate to  
11 present at this time, I mean, because they're all questions.

12 CHAIRMAN FROINES: Sure.

13 And the workshop was successful insofar as it  
14 actually demonstrated the wide range of issues that we have  
15 before us and will have implications beyond  
16 organophosphates.

17 DR. HOWD: Yes.

18 CHAIRMAN FROINES: So Dr. Blanc is here. Welcome.

19 DR. BLANC: Thank you. Sorry.

20 CHAIRMAN FROINES: He's yawning. He's ready to  
21 take a nap.

22 DR. FUCALORO: Ready for lunch.

23 CHAIRMAN FROINES: Thanks very much. That was  
24 very helpful and I think it's a good first step.

25 So we're just as a scheduling issue, the plans

1 were to break for lunch now, the panel will take a 45-minute  
2 lunch. After lunch the first thing we'll take up will be an  
3 executive session to discuss the legal suits.

4 I think then after the discussion with the  
5 attorneys is over, we'll go back and finish the items 3 and  
6 4 with time permitting, so that the members of the  
7 representatives --

8 DR. FUCALORO: Items 2 and 3.

9 CHAIRMAN FROINES: 2 and 3, sorry.

10 So that I suspect that other representatives from  
11 the various agencies probably are going to have an hour and  
12 45-minute lunch.

13 DR. FUCALORO: Life is wonderful.

14 CHAIRMAN FROINES: So why don't we break at this  
15 point, and then so for everyone else we should be back  
16 here -- you should be back here about -- I'm not smart  
17 enough to do that.

18 DR. FUCALORO: We should be back at 1:00.

19 CHAIRMAN FROINES: About 1:00, and the rest come  
20 back about 2:00.

21 (Thereupon the lunch recess was taken.)

22 CHAIRMAN FROINES: If I can break into the  
23 post-lunch levity, I have to make a statement, which I've  
24 forgotten the actual details on, but I think it says that  
25 the panel is meeting with legal representatives from the

1 attorney general's office and from the Air Resources Board  
2 to discuss litigation involving the panel, and no one is  
3 here in the room with the exception of our legal  
4 representation, the legal representatives and the panel.

5 Thank you.

6 (Pause in proceedings.)

7 CHAIRMAN FROINES: The cases are, one, metam  
8 sodium task force versus John R. Froines, et al, Superior  
9 Court, Sacramento, case number 00AS04636.

10 Two, request for determination concerning the  
11 Office of Environmental Health Hazard Assessment and the  
12 Scientific Review Panel, range of unit risk values for  
13 particulate emissions from diesel-fueled engines established  
14 by OEHHA, specific unit risk factor for diesel-fueled  
15 engines adopted by SRP, file number 99-026.

16 The panel -- that's it.

17 The panel will hold a closed session as authorized  
18 by Government Code 11126, subdivisions (e)(1) and (e)(2)(A)  
19 to confer with or receive legal advice -- advice from legal  
20 counsel regarding this litigation.

21 (Pause in proceedings.)

22 MR. REEVES: Bruce Reeves, from the State of  
23 California Attorney General's office.

24 The request for determination concerning the OEHHA  
25 and SRP unit risk factors will also extend to the judicial

1 litigation over that same issue, entitled Apodaca versus  
2 California Air Resources Board, et al.

3 (Thereupon the panel went into closed session  
4 at 1:17 p.m.)

5 CHAIRMAN FROINES: The executive session to  
6 discuss the litigation -- do I have to go through all the --  
7 the executive session discussing the litigation pending with  
8 the Scientific Review Panel came to a close at 3:52 p.m.

9 DR. WITSCHI: I make a motion the meeting be  
10 adjourned.

11 DR. FRIEDMAN: I second it.

12 CHAIRMAN FROINES: All in favor.

13 We don't have a quorum -- yes, we do. Pardon me.

14 Meeting is officially adjourned.

15 (Thereupon the meeting was adjourned  
16 at 3:53 p.m.)

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2

3 I, JANET H. NICOL, a Certified Shorthand Reporter  
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8 I further certify that I am not of counsel or  
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